gas and various petroleum products. It has been used as a filler in rubber, plastics, phonographic records, and inks[267] and in the manufacture of carbon paper and carbon electrodes. The importance of carbon black as a cause of pulmonary disease is unclear. Although examples of pneumoconiosis attributed to heavy exposure during the manufacture of such products had been reported rarely before 1990,[267, 268, 286] a 1993 survey of carbon black workers in seven European countries, including more than 1,000 for whom chest radiographs were available, revealed the presence of reticular abnormalities in 25%.[287] The likelihood of identifying these abnormalities was related to total cumulative dust exposure. By contrast, in a report of the results of a survey of process workers in a factory producing continuous filament carbon fiber, no evidence of ill effects on the lungs was found by radiographic, spirometric, or clinical assessments.[288] Similar results were demonstrated in a factory in which activated charcoal was manufactured, in which workers had been exposed to pure carbon dust for up to 11 years.[289]

Pathologic, radiographic, and clinical findings in workers exposed to large amounts of carbon in whatever form are similar; however, because the vast majority of such individuals are involved in coal mining, most of the reported literature and much of the following description relate to CWP.

Pathogenesis

The precise pathogenetic factors involved in the development of simple CWP and complicating PMF are unclear, and several agents or processes, either alone or in combination, may be responsible. As might be expected, the most important factor may be the quantity of inhaled coal. The prevalence of CWP and the risk of progressing to a higher category of simple pneumoconiosis are both related to cumulative dust exposure.[283, 290, 291] Similarly, PMF is more likely to occur in workers who have had heavy dust exposure and who have large amounts of dust in their lungs at autopsy.[291–296] Although the major effect of dust is its influence on the development of CWP, even workers who do not have radiologic evidence of CWP have an increased risk of developing PMF with increasing dust exposure.[291] Associated tuberculosis may be important in determining progression to PMF in China, where the infection is particularly prevalent;[297] however, it appears to play little role in other regions. The results of more recent studies have confirmed the importance of higher profusion category[298, 299] and younger age at diagnosis of CWP[298] as risk factors for the subsequent development of PMF. One group of investigators found patients who were lighter in weight for their height to be at increased risk for PMF.[298] A high degree of correlation between the presence of PMF and the degree and type of pathologic abnormality in perihilar lymph nodes has also been described.[300]

Because PMF in patients with silicosis is similar both pathologically and radiologically to that in patients who have CWP, it has been suggested that contamination of coal dust by silica may be responsible for the lesion in the latter individuals.[301] A number of findings argue against this hypothesis, however, including (1) the observation that there is a wide variation in the amount of silica in the lungs of coal workers who have PMF;[271] (2) the finding in at least some studies that the severity of CWP is more closely related to total carbon content of the lung than to the concentration of silica;[302] and (3) the observation that workers who are exposed almost exclusively to carbon, such as those involved with carbon black or carbon electrodes, can develop lesions identical to those that occur in underground coal workers.[263, 266–268, 286]

These observations have, in turn, been challenged. For example, it has been speculated that there may be differential clearance and enhanced retention of silica in mixed dust exposures, allowing for an effect disproportionate to its inhaled concentration.[303] In addition, critical analysis of many of the articles claiming to report pure carbon exposure has shown that their determinations of the composition of inhaled dust can be faulted. In fact, silica as well as other minerals mixed with inhaled coal dust may influence the body's response to this dust mixture in a complex and as yet ill-defined fashion. For example, in one study of the lungs of 490 British coal miners, investigators found evidence for two distinct histologic varieties of PMF, one apparently formed by conglomeration of several nodular lesions and the other by enlargement of a single lesion.[301] The two patterns were associated with different degrees of lung dust content and colliery rank, and the authors suggested that the effect of silica (perhaps itself affected by the presence of other inhaled substances, such as kaolinite and mica) might be important in pathogenesis.

An understanding of the cellular and molecular basis of CWP is also incomplete, in part because of a failure to distinguish between the effects of carbon and the effects of contaminating silica and other elements present in coal dust. Similar to silicosis, CWP is associated with the production of oxidants,[304, 305] probably derived predominantly from alveolar macrophages.[306] Compared with that from healthy individuals, BAL fluid from patients who have CWP has revealed lymphocytosis; evidence of increased alveolar permeability; increased IL-6, TNF-α,[307] type I insulin-like growth factor (IGF-1), fibronectin,[93] and platelet-derived growth factor (PDGF);[308] and decreased interferon-γ.[309] As in other diseases, the functions of these cytokines are varied and their interaction complex; for example, the overall role of IL-6 may be an antifibrotic one,[309] whereas IGF-1 and PDGF appear to promote fibrosis.[308] Other cytokines are also likely to be important in pathogenesis; for example, peripheral monocytes of miners who have CWP have been shown to have enhanced release of TNF-α, which can stimulate the adhesion of polymorphonuclear neutrophils to endothelium, stimulate fibroblast growth, and induce production and release of IL-1 and reactive oxygen species from mononuclear phagocytes.[310, 311]

The presence in coal miners of hypergammaglobulinemia,[312] rheumatoid factor, and antinuclear or antilung antibodies has also raised the possibility of an immunologic mechanism in the pathogenesis of CWP. Although some investigators have found titers of rheumatoid factor and autoantibodies to be higher than those in control subjects before the development of radiographic abnormalities,[313] most have shown them to rise with increasing severity of radiographically determined category of disease.[313–318] In one study, the prevalence of antilung antibodies and lymphocyte-

mediated cellular cytotoxicity was found to be higher in smoking than in nonsmoking miners.[319]

Caplan[320] originally reported the association between rheumatoid arthritis and CWP. In addition, Caplan and colleagues[316] described an increased incidence of rheumatoid factor in miners who had the r type of small rounded opacities as well as in patients who had irregular, large opacities unassociated with overt rheumatoid arthritis. Other workers have confirmed and extended these observations. For example, in one investigation of 109 coal workers who had pneumoconiosis, circulating antinuclear antibody and rheumatoid factor were found in almost 15% of miners who had simple pneumoconiosis and 45% of those who had category C PMF.[314] Other workers have shown positive test results for rheumatoid factor in 30% to 40%[315] and for antinuclear antibodies in 75%[317] of patients who have PMF. One group also demonstrated the presence of rheumatoid factor to be a marker for more rapid progression of pneumoconiosis.[321] In addition, lung-reactive antibodies have been identified in the serum of miners[322] and in rats and mice exposed to coal dust.[323] Although positive titers of all these serum antibodies are not in the same range as those found in connective tissue diseases, in most cases their level has been recorded as at least 1/10, a finding observed in only 2% to 3% of the normal male population.[314]

Three groups of investigators have failed to reveal an association between either simple or complicated CWP and any specific histocompatibility antigen;[324–326] however, another group showed the more rapid development of CWP in miners who had HLA DRB8 and resistance to the development of CWP in those who had DRB1 and DRB2.[327] Despite this abundant evidence suggesting a role for immunologic factors in the development of PMF, the details of possible pathogenetic mechanisms are not understood.

Pathologic Characteristics

The two morphologic findings characteristic of CWP are the coal macule and PMF.[271, 328, 329] The former is characterized by deposits of anthracotic pigment unassociated with fibrosis, a finding sometimes referred to as *simple* pneumoconiosis. PMF is defined as a focus of fibrosis and pigment deposition larger than 1 cm in diameter and is sometimes designated *complicated* pneumoconiosis. In addition, smaller foci of fibrous tissue (so-called nodular lesions) can be found in many cases, either with or without features of PMF.[271, 329]

Grossly, coal macules are stellate or round, nonpalpable foci that are black and range in size from 1 to 5 mm (Fig. 60–21). They are scattered fairly uniformly throughout the lung parenchyma, although they tend to be more numerous at the apex than at the base. In uncomplicated disease, lung

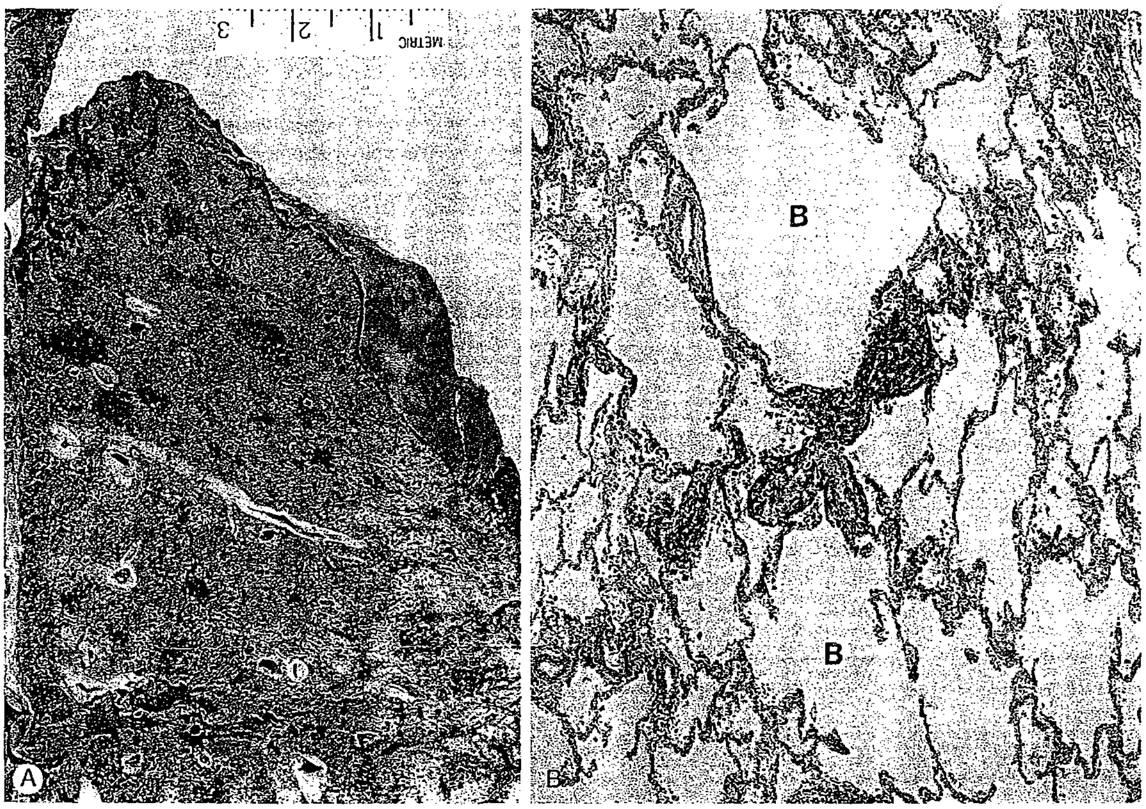

Figure 60–21. Coal Workers' Pneumoconiosis: The Coal Macule. A magnified view *(A)* of the superior segment of a lower lobe shows multiple foci of dense black pigmentation that are of irregular shape but are fairly evenly spaced. Emphysema is present but is difficult to appreciate in this thick, formalin-fixed section. Note also the dense zone of subpleural pigment deposition. A histologic section *(B)* shows numerous alveolar macrophages containing abundant anthracotic pigment situated in the interstitial tissue adjacent to respiratory bronchioles (B). No fibrosis is evident. The bronchioles are moderately dilated. (×40.)

tissue between the macules is typically normal in structure and color, although interlobular septa and peribronchial connective tissue and lymph nodes are also usually heavily pigmented. Microscopically, the macule consists of numerous pigment-laden macrophages in the interstitial tissue adjacent to respiratory bronchioles (*see* Fig. 60–21); reticulin fibers can be identified between the macrophages, but mature collagen is minimal or absent. Aggregates of pigment-laden macrophages can also be seen in adjacent alveolar air spaces, especially in lung tissue derived from active miners. Bronchioles within the macules are frequently distended (*see* Fig. 60–21), a finding often designated *focal emphysema*.[281, 330] Depending on the type of coal or form of carbon dust that has been inhaled,[271] the particulate material within the macrophages differs somewhat in shape, size, color, and translucency. Ferruginous bodies composed of coal can be identified occasionally (Fig. 60–22); they are similar to those that occur with asbestos exposure except for the presence of relatively large, black cores.

Although the coal macule is characteristic of CWP, identical lesions can be found in individuals from other environments,[261] and the simple presence of a macule does not constitute definite evidence of occupational dust exposure. Microscopic foci of macrophage aggregates similar to those in the coal macule can also be identified in regional lymph nodes and occasionally outside the thorax in tissues such as bone marrow.[331]

Palpable gray or black nodules smaller than 1 cm in

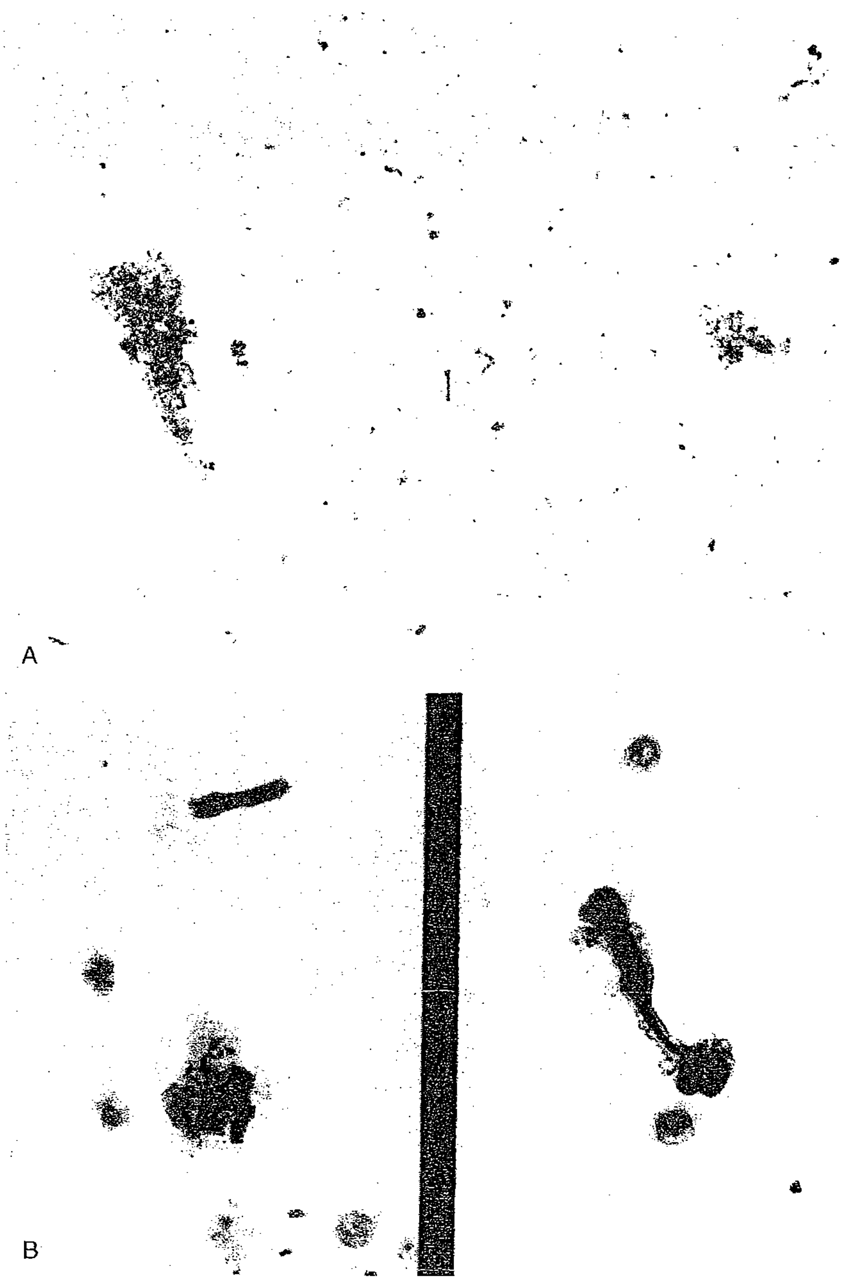

Figure 60–22. Coal Workers' Pneumoconiosis: Transthoracic Needle Aspirate. A filter preparation from a transthoracic needle aspirate *(A)* shows single and clustered cells, many of which appear to contain foreign material. Magnified views of two foci *(B)* show this material to be black, irregular in shape, and localized both within macrophages (on the left) and free (on the right). The latter particle is a ferruginous body, consisting of a central black core (representing the coal particle) and a transparent somewhat nodular iron-protein coat. This material was aspirated from a patient who had an upper lobe mass that resembled a carcinoma. (*A*, ×100; *B*, ×800; Papanicolaou stain.)

diameter can also be found in the lungs of many coal workers. Although these are described separately, they blend imperceptibly with the macule on the one hand and with PMF on the other,[301] and it is likely that they represent part of a spectrum of changes rather than pathogenetically distinct lesions. The nodules can be stellate or round and are fairly well delimited from adjacent lung. They have a variable histologic composition, some consisting of a haphazard mixture of pigment-laden macrophages, free dust, and reticulin and collagen fibers (Fig. 60–23) and others possessing a relatively discrete central zone of pigment-free collagen surrounded by pigment-laden macrophages resembling small silicotic nodules. Degenerative changes identical to those seen in PMF are present occasionally.[271] Other palpable nodules, such as rheumatoid nodules of Caplan's syndrome (*see* page 2416) and infectious granulomas, are seen less frequently.

The lesions of PMF are firm or somewhat rubbery in consistency and either round or irregular in shape. They may be unilateral or bilateral and develop most often in the posterior segment of an upper lobe or superior segment of a lower lobe,[268, 332, 333] a localization that is thought by some to be related to poor lymphatic drainage.[334] A lesion can extend across the pleura into an adjacent lobe or mediastinum. Adjacent emphysema is not uncommon. Cut sections often reveal a necrotic center containing black fluid that can be washed away, leaving a cavity. In most cases, the pathogenesis of the necrosis is ischemia;[335, 336] vascular obliteration both within and adjacent to the region of PMF is a common histologic finding (*see* farther on), and avascular zones can be demonstrated by lung perfusion scanning.[337] Occasionally, cavitation is caused by tuberculous infection.

The microscopic features of PMF are similar to those of the smaller palpable nodules already described. Bundles of haphazardly arranged, sometimes hyalinized bands of collagen are interspersed with numerous pigment-laden macrophages and abundant free pigment; the latter tends to be more evident in the central regions.[338] Foci of degenerated and frankly necrotic tissue, cholesterol clefts, and mononuclear inflammatory cells are often present. Although the hyalinized tissue is usually assumed to be collagen, biochemical analysis has shown a high proportion of a noncollagenous, insoluble protein,[339] at least some of which is probably fibronectin.[340] Airways and blood vessels can be incorporated within and destroyed by the expanding fibrotic process (Fig. 60–24), and vessels at the periphery of the lesion frequently show endarteritis obliterans.

Cor pulmonale is common at autopsy of patients who have complicated CWP and is occasionally seen in those who have the simple form of the disease.[341–343] In most patients in the latter group, this complication can be explained on the basis of associated chronic obstructive pulmonary disease or silicosis.

Pathologic features of pneumoconiosis associated with graphite and carbon black exposure are similar to those of CWP except that the complicating effects of silica that may be seen with the latter are typically absent. Graphite crystals may be coated with deposits of iron and protein (ferruginous bodies) and can be identified in tissue sections and by digestion techniques.[344, 345]

Radiologic Manifestations

The radiographic pattern of simple pneumoconiosis is typically one of small, round opacities (nodular).[346–348] Occasionally—particularly in the early stages—it is predominantly reticular (small irregular opacities) or reticulonodular (Fig. 60–25).[349] The nodules range from 1 to 5 mm in diameter, tend to be somewhat less well defined than those of silicosis, and have a "granular" density in contrast to the homogeneous density of silicotic nodules. Radiographic-

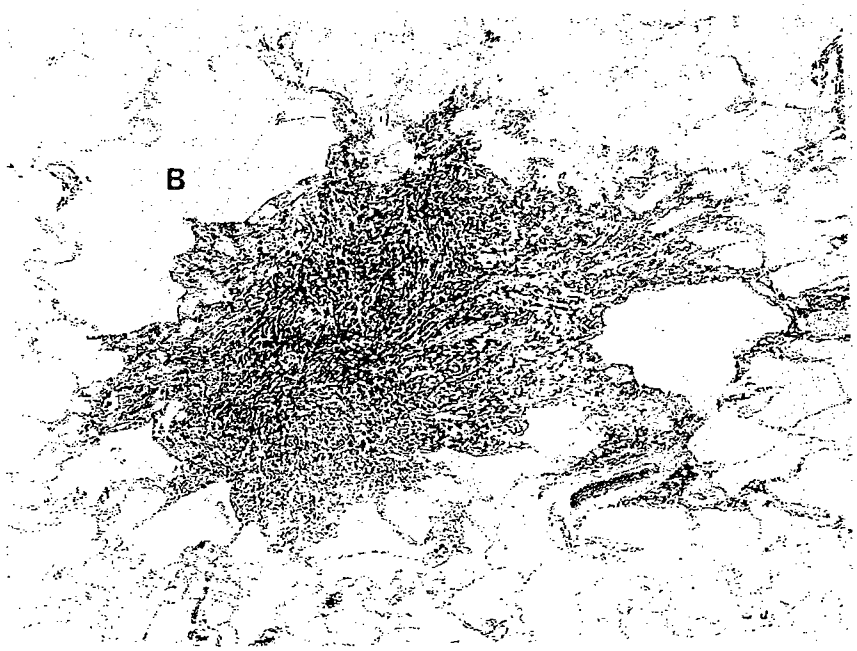

Figure 60–23. Coal Workers' Pneumoconiosis: Nodular Lesion. A histologic section shows a stellate focus of pigmented macrophages adjacent to two respiratory bronchioles, one of which is mildly dilated (B). Connective tissue stains showed abundant reticulin fibers but only mild collagen deposition. In contrast to the typical coal macule, this lesion was palpable. (×40.)

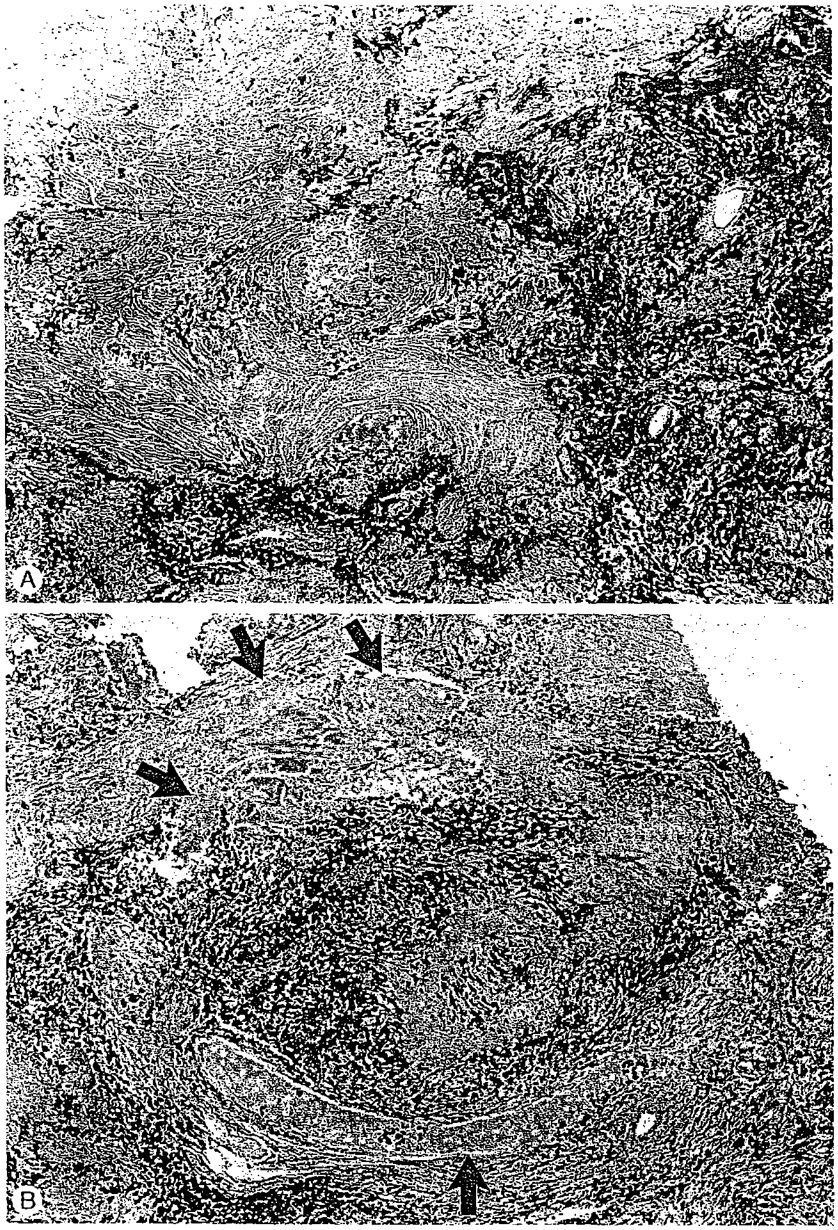

Figure 60–24. Coal Workers' Pneumoconiosis: Progressive Massive Fibrosis. A histologic section *(A)* from a 4-cm mass in the upper lobe of a retired coal worker shows abundant anthracotic pigment as well as extensive collagen deposition. No necrosis is evident. At slightly higher magnification, another focus *(B)* shows the lumen of a subsegmental bronchus completely obliterated by similar tissue (*arrows* denote residual, partly destroyed cartilage plates). (*A*, ×25; *B*, ×35.)

pathologic correlative studies suggest that the opacity of individual nodules cannot be entirely attributed to the coal dust, whose density is only slightly greater than unity.[350] Despite these observations, it is generally agreed that the radiographic manifestations of CWP cannot be distinguished from those of silicosis with any degree of confidence.

Calcification of pulmonary nodules is identified radiographically in 10% to 20% of older coal miners, particularly anthracite workers.[351, 352] The calcification begins as a central dot, thus helping to differentiate these nodules from those of silicosis, in which the calcification tends to be diffuse. Eggshell calcification is uncommon; for example, in one study of 1,063 coal miners whose chest radiographs showed evidence of pneumoconiosis, it was evident in only 1.3%, all of whom had worked 20 or more years in the mines.[351]

The appearance of large opacities indicates the development of complicated pneumoconiosis (PMF). These lesions range from 1 cm in diameter to the volume of a whole lobe in aggregate. Although most commonly restricted to the upper half of the lungs, they may also occur in the lower lung zones (Fig. 60–26). They are usually observed on a background of simple pneumoconiosis but have been found to develop in miners whose initial chest radiographs 4 to 5 years earlier were considered to be within normal limits.[353] The complication is said to occur in about 30% of patients who have diffuse bilateral opacities.[280, 354] It typically starts near the periphery of the lung and is manifested as a mass that has a well-defined lateral border that parallels the rib cage and projects 1 to 3 cm from it.[351] The medial margin of the mass is often ill-defined in contrast to its sharp lateral

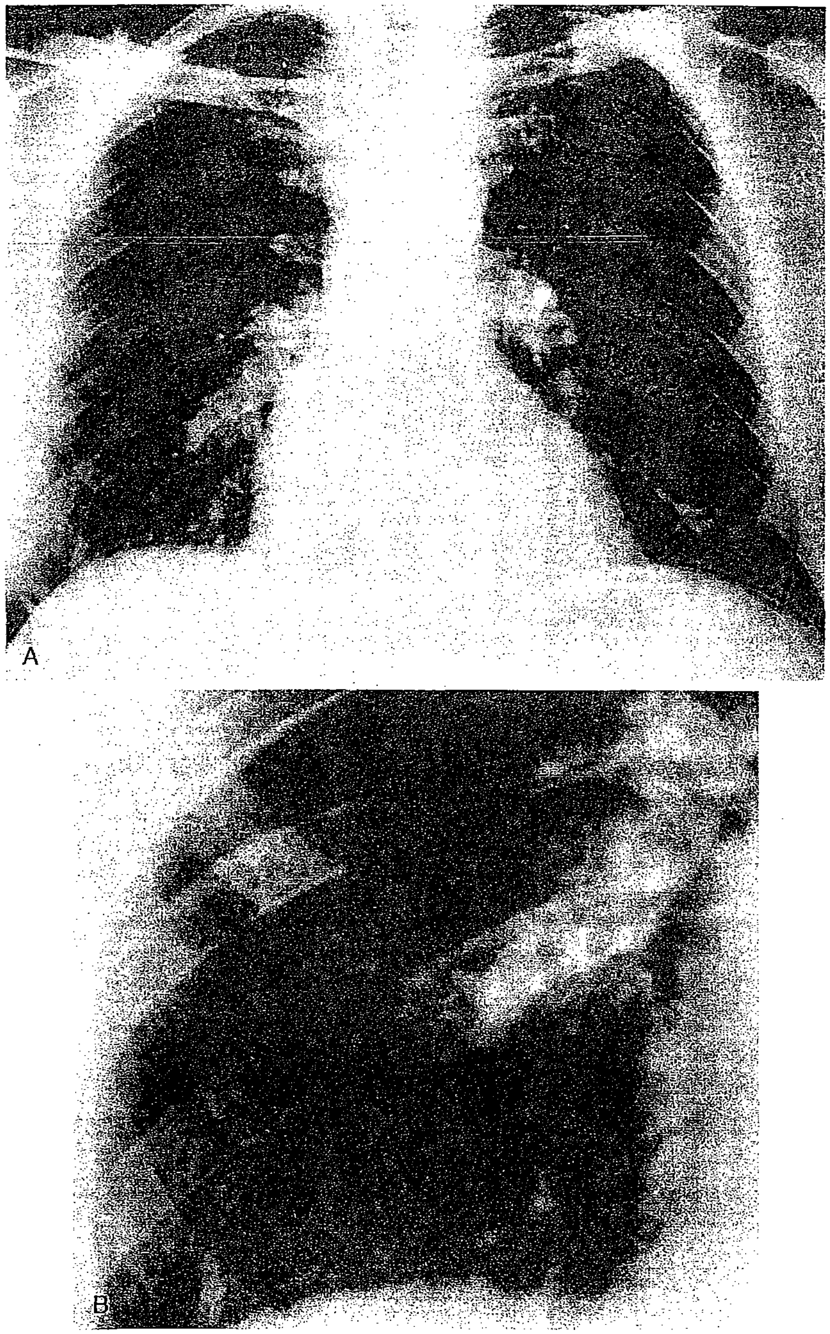

Figure 60–25. Coal Workers' Pneumoconiosis. This posteroanterior radiograph *(A)* and magnified view of the lower half of the right lung *(B)* reveal a coarse reticulonodular pattern throughout both lungs, affecting the upper lung zones least. Both hila are enlarged and possess a contour suggestive of lymph node enlargement. The patient, a 45-year-old miner, was admitted to the hospital complaining of increasing shortness of breath. Approximately 15 years previously, he had worked underground in a Belgian coal mine for 7 years and had been exposed to heavy concentrations of dust but had never worn a mask. At the time of admission, he stated that he was short of breath after walking 100 yards on level ground or climbing 7 to 10 steps. Pulmonary function studies were within normal limits except for a slight reduction in functional residual capacity; studies of lung mechanics revealed normal compliance and airway resistance.

border, a configuration that was observed in 22 of 50 coal miners in one study.[351] The masses of PMF tend to be thicker in one dimension than the other; for example, they tend to produce a broad face on a posteroanterior radiograph and a thin shape on a lateral radiograph, frequently paralleling the major fissure.[351] As might be expected, this spindle-shaped configuration creates a radiographic opacity that is considerably less dense in one projection than in the other. PMF is usually homogeneous in density, unless cavitation has developed. This complication occurs only occasionally; it may develop after exposure to coal dust has ceased and, in contrast to simple pneumoconiosis, may progress in the absence of further exposure.[280, 347, 355]

As with the conglomerate shadows of silicosis, PMF usually originates in the lung periphery and gradually migrates toward the hilum, leaving a zone of emphysematous lung between it and the chest wall. Particularly when unilateral, a large mass may closely simulate pulmonary carcinoma. Because PMF is occasionally unassociated with radiographic evidence of nodularity,[351] the correct diagnosis in these cases may not be suspected in the absence of an appropriate occupational history. The smooth, sharply de-

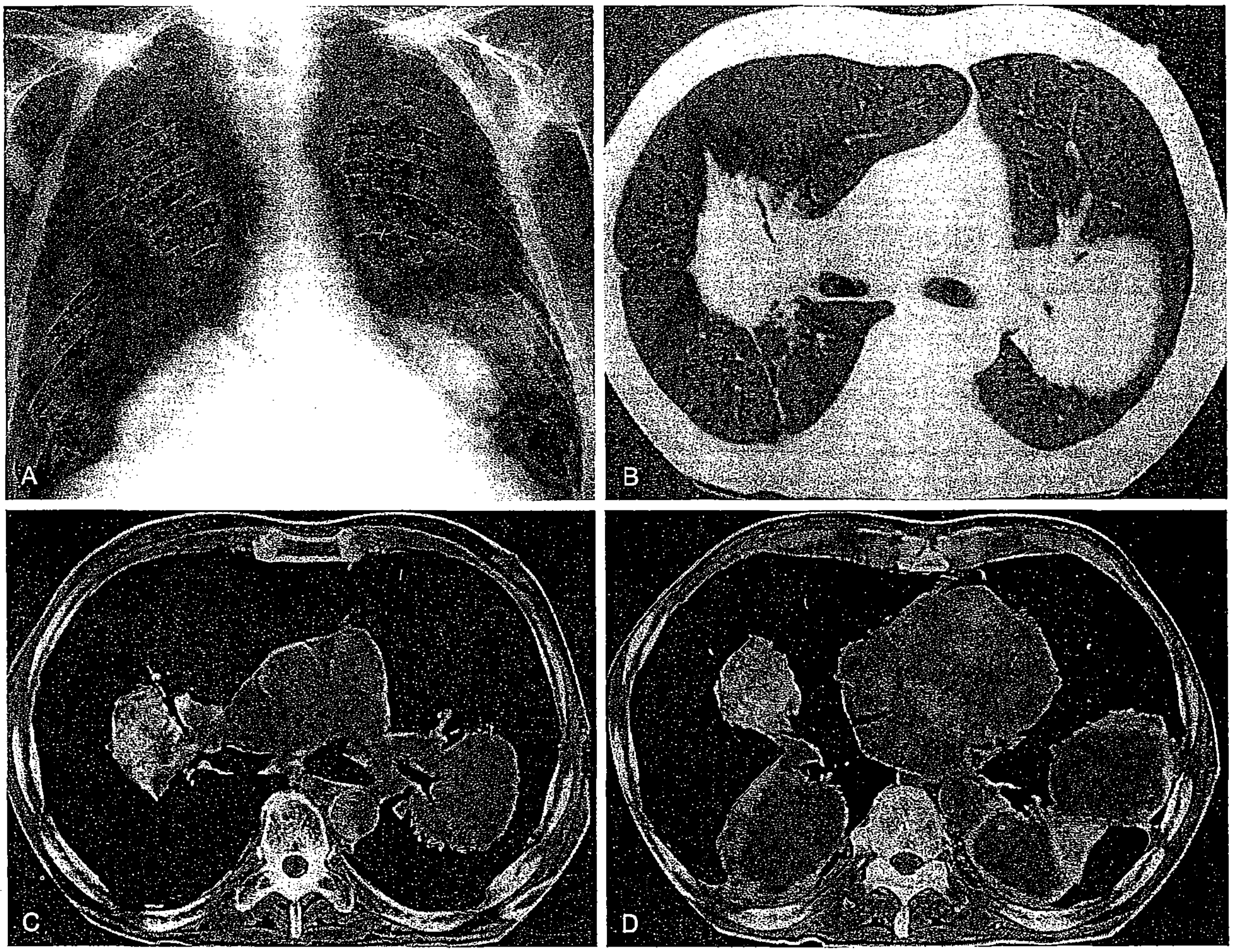

Figure 60–26. Coal Workers' Pneumoconiosis with Conglomerate Masses. An anteroposterior chest radiograph *(A)* shows large opacities in the middle and lower lung zones. A 10-mm collimation CT scan at the level of the right upper lobe bronchus *(B)* demonstrates bilateral perihilar conglomerate masses. Irregular linear opacities and distortion of lung architecture indicative of fibrosis and emphysema are also evident. Soft tissue windows *(C* and *D)* demonstrate that three of the conglomerate masses have large central areas of decreased attenuation suggestive of necrosis. The patient was a 65-year-old man with a 30-year history of exposure to coal dust. (Courtesy of Dr. Martine Remy-Jardin, Centre Hospitalier Regional et Universitaire de Lille, Lille, France.)

fined lateral border and the somewhat flattened configuration characteristic of these lesions are useful clues in differentiation from a pulmonary carcinoma, whose borders tend to be less well defined and whose configuration is typically spherical. Occasionally, a lesion of PMF contains foci of calcification, an obvious additional aid in radiographic differential diagnosis. Linear calcification may also be seen along the border of an area of PMF, invariably along the lateral margin.[351]

Caplan's syndrome consists of the presence of necrobiotic nodules associated with rheumatoid arthritis superimposed on a background of inorganic dust exposure (*see* page 1438).[320] The nodules are more regular in contour and more peripherally located than the masses of PMF (Fig. 60–27). They range in size from 0.5 to 5 cm in diameter and are seen most often in workers who have subcutaneous rheumatoid nodules and whose chest radiographs are classified as category 0 or 1 simple pneumoconiosis.

In contrast to similar comparisons in silicosis, the radiographic findings correlate well with pathologic abnormalities in CWP.[350, 356] The effects of film quality and other factors on the radiographic categorization of the disease have been analyzed in several studies.[357-359]

The CT findings of CWP are similar to those of silicosis and consist of small nodules that may be seen diffusely throughout both lungs but are most numerous in the upper lung zones.[190, 360, 361] In patients who have mild disease, the nodules may involve only the upper lung zones and show a posterior predominance.[360] A random distribution is typical, although in some cases HRCT may demonstrate a centrilobular predominance.[193, 360] Subpleural nodules are seen in approximately 80% of patients who have other parenchymal nodules. Confluence of such nodules may result in linear areas of increased attenuation a few millimeters wide (pseudoplaques).[193] Correlation of HRCT with pathologic specimens has demonstrated that these subpleural micronodules may also be associated with localized thickening of the visceral pleura as a result of fibrosis.[362] Calcification of

Figure 60–27. Caplan's Syndrome. Posteroanterior *(A)* and lateral *(B)* radiographs reveal a multitude of fairly well-circumscribed nodules ranging in diameter from 1 to 5 cm, scattered randomly throughout both lungs with no notable anatomic predilection. No cavitation is apparent, and there is no evidence of calcification. This patient, a 56-year-old man, had been a coal miner for many years and in recent years had developed arthralgia, which proved to be due to rheumatoid arthritis. As a means of establishing the nature of the pulmonary nodules, a percutaneous needle aspiration was carried out on the large mass situated in the lower portion of the left lung *(arrowheads in A):* Several milliliters of inky black fluid were aspirated.

nodules can be identified in approximately 30% of patients. Hilar or mediastinal lymphadenopathy is also seen in about 30% of cases; the majority of enlarged nodes are calcified.[360]

Large opacities (PMF) in patients who have CWP usually have irregular borders associated with distortion of the surrounding lung architecture and emphysema.[193, 360] Less commonly, they have regular borders and are unassociated with emphysema.[360] The large opacities occur most commonly in the upper lung zones and, although frequently bilateral, may be unilateral (most commonly in the right upper lung zone).[360]

CT has been shown by several investigators to be superior to chest radiography in the detection of small nodules.[190, 360, 361] Conventional CT and HRCT are considered to be complementary in assessment (Fig. 60–28).[193, 360] In one prospective study of 170 coal dust–exposed workers, posteroanterior and lateral chest radiographs, contiguous conventional (10-mm-thick sections) CT scans, and HRCT scans (2-mm-thick sections) at five selected levels were compared.[360] Findings consistent with CWP were detected on CT in 11 of 48 (23%) workers who had no evidence of pneumoconiosis on chest radiographs (ILO profusion score < 1/0); in some patients whose radiographs were interpreted as showing findings consistent with pneumoconiosis, CT showed the abnormalities to consist of bronchiectasis or emphysema, rather than the macules of CWP.

Clinical Manifestations

Symptoms of cough, sputum production, and dyspnea are more common in miners who have early CWP than in miners who have similar smoking and dust exposure histories but no radiographic evidence of disease.[363] These symptoms are even more frequent and severe in workers who have PMF, who also suffer from recurrent attacks of purulent bronchitis. Copious amounts of black sputum may be produced when an ischemic lesion of PMF liquefies and ruptures into a bronchus ("melanoptysis"), in which circumstance a cavity should be visible radiographically.[364–366] With progression of the disease, dyspnea usually worsens; cor pulmonale and right-sided heart failure may ensue.

The degree of breathlessness appears to be directly related to the stage of the disease. In patients who have simple pneumoconiosis, there is usually no breathlessness on exertion despite increasing radiographic abnormality, unless there is associated emphysema. By contrast, in those who have complicated disease, breathlessness is nearly always severe and increases with progression of radiographic changes.[367] Physical examination may reveal decreased breath sounds and a few crackles. A patient has been described who developed vocal cord paralysis as a result of impingement of PMF on the recurrent laryngeal nerve.[368] As in silicosis, the risk of developing tuberculosis is increased in workers who have CWP;[271, 369] for example, a survey of Spanish coal miners, both with and without pneumoconiosis, revealed a risk of developing the infection three times that of the general surrounding population.[256]

There is little doubt that coal dust inhalation is related to the development of emphysema and chronic air-flow obstruction;[370] in addition, coal workers appear to be susceptible to chronic bronchitis.[371–374] In several investigations, emphysema has been shown to be present more often and to be more severe in patients who have CWP than in those who do not;[375, 376] emphysema also correlates with the degree of exposure to coal dust[377] and is additive to the effects of cigarette smoking.[294, 378, 379] In one investigation, nonsmokers who had experienced intermediate and high dust exposure levels had the same prevalence of abnormal lung function as smokers who had no dust exposure.[374] In one autopsy

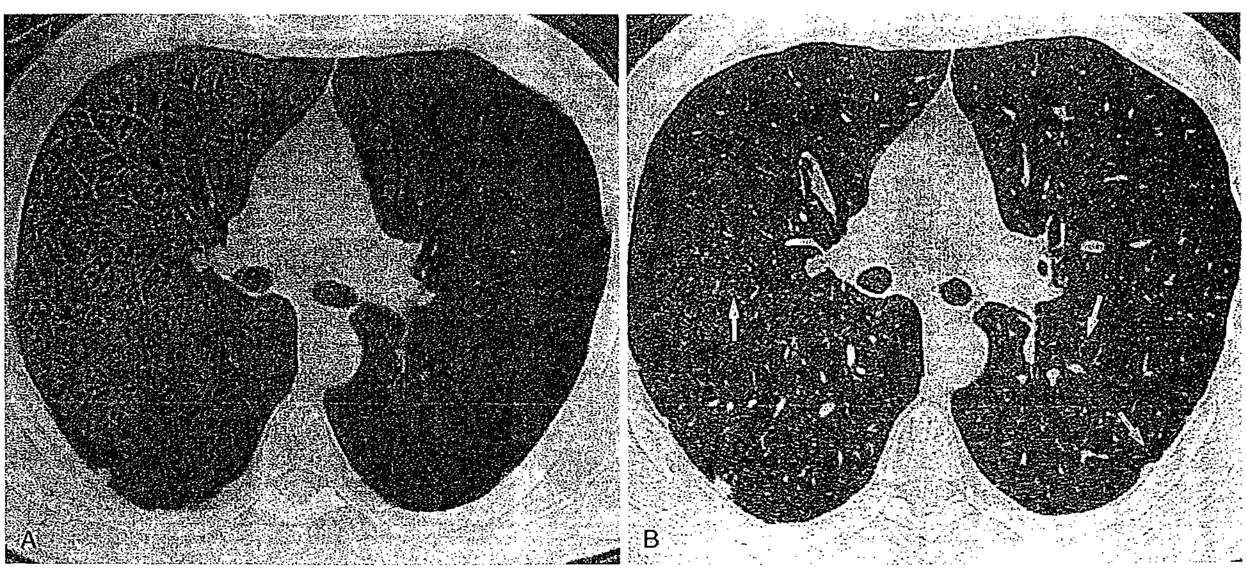

Figure 60–28. Coal Workers' Pneumoconiosis: Conventional CT and HRCT Findings. A conventional 10-mm collimation CT scan *(A)* demonstrates small nodules in both lungs. Subpleural nodules mimicking pleural plaques are also evident posteriorly. On HRCT *(B)*, the nodules are more difficult to distinguish from vessels. The nodular and branching opacities, however, clearly have a centrilobular distribution *(arrows)*. The subpleural pseudoplaques are also better defined on the HRCT image. (Courtesy of Dr. Martine Remy-Jardin, Centre Hospitalier Regional et Universitaire de Lille, Lille, France.)

study, the prevalence of emphysema was found to be greater in patients who had an increased severity of pneumoconiosis.[380] In a second such study, a strong association was also identified between dust content and emphysema in both nonsmokers and smokers.[381] Dust exposure and impairment of lung function were also linked in two large groups of American coal miners,[382, 383] although these results have been criticized because of poor validation of dust exposures.[384]

Laboratory Findings

Gallium scanning and labeled diethylenetriamine pentaacetate (DTPA) uptake are both abnormal in workers who have CWP,[385] reflecting the presence of lung injury and inflammation. The acute phase reactants C-reactive protein and fibrinogen are also elevated;[386] whether monitoring their levels serves any useful purpose remains to be determined. In one investigation, measurement of serum procollagen III was not found to be helpful in predicting progression of disease.[387] As indicated previously, hypergammaglobulinemia[312] and elevated serum levels of rheumatoid factor and antinuclear antibodies are common.[313–318]

Pulmonary Function Tests

Published results of pulmonary function testing in coal workers are variable, largely because of differences in population groups studied. Retired miners generally show more impairment than those who are working, an apparent paradox that is presumably explained by the observation that the former tend to leave their job because of disability (the appreciation of good lung function in working miners being an example of the "healthy worker" effect). Other variables that influence results include cigarette smoking and the particle size of coal dust inhaled.

One often cited study of pulmonary function published in 1955 involved patients who had simple pneumoconiosis and a control group of the same age; apart from minor disturbances in gas distribution, no significant differences in function were identified.[388] The results of a more recent long-term follow-up study of coal miners who did not have PMF but who were suspected of having suffered greater than average effects from dust exposure showed a relationship between exposure and FEV_1;[295] this suggests that even moderate exposure to dust can cause severe impairment of lung function in some miners. This hypothesis has been supported by the results of other studies in which a deterioration in FEV_1 has been shown to be related to cumulative dust exposure in coal workers whose chest radiographs were normal.[294, 389] In another investigation, patients who had radiographic changes suggestive of early disease (ILO classification 0/1 or 1/0) and CT scans that confirmed the presence of such disease, had lower $FEV_{1.0}/FVC$ ratios than similarly exposed individuals who had normal radiographs.[414]

Diffusing capacity can be reduced in miners who smoke but is usually normal in nonsmoking miners who have simple pneumoconiosis.[390, 391] Focal impairment of $\dot{V}/\dot{Q}$ ratios resulting in impaired gas exchange has been described in nonsmoking coal miners despite normal spirometric findings.[392] One assessment of lung mechanics in the early stages of simple CWP has shown a loss of elastic recoil, implying the presence of emphysema.[393] Reduced diffusion, impaired gas exchange, and pulmonary hypertension have been described in coal workers who manifest category p micronodular disease.[280, 394–396] In a correlative radiographic, physiologic, pathologic, and clinical study of 247 coal miners, extensive emphysema was more common in patients who had this micronodular pattern than in those who had larger nodules, whether the pneumoconiosis was simple or complicated.[375] Other investigators have related the development of physiologic obstruction and emphysema to the late appearance of small irregular opacities (type s or t).[347, 348, 397]

In contrast to simple CWP, PMF is frequently associated with physiologic evidence of airway obstruction, reduced diffusing capacity, abnormal blood gases, and increased pulmonary arterial pressures.[398, 399] In one investigation, changes in function were attributed not only to PMF and the extent of emphysema, but also to small airway disease and interstitial fibrosis.[400] A comparison of pulmonary function in coal workers who had Caplan's syndrome and those who had PMF showed significantly less obstruction in the former patients but no significant difference in DLCO.[401]

Prognosis and Natural History

Mortality studies in coal miners[402] and coke oven workers[403] have shown no increase in the standardized mortality rate, despite an increase in the incidence of death from respiratory disease; in both these studies, this apparent paradox was explained on the basis of a significant decrease in the incidence of death from heart disease. Other investigators, however, have shown modest reductions in survival of men who have simple CWP,[404, 405] partly as a result of chronic obstructive pulmonary disease. Workers who have higher degrees of PMF, both smokers and nonsmokers, have significantly increased mortality rates.[406] In one investigation, miners who developed PMF when young had one third the survival rate of those who do not have CWP after a 22-year period of observation.[404] In contrast to patients who have silicosis, coal workers who have simple pneumoconiosis seldom show progression of disease if removed from the dust-ridden environment.[407, 408]

ASBESTOS

Asbestos is the general term given to a group of fibrous minerals composed of combinations of silicic acid with magnesium, calcium, sodium, and iron. The word is derived from the Greek, meaning *inextinguishable*,[409] reflecting the resistance of the substance to heat and acid as well as its strength, durability, and flexibility.

Mineralogically, asbestos can be divided into two major groups: the *serpentines*, of which the only member of commercial importance is chrysotile, and the *amphiboles*, which include amosite (brown asbestos), crocidolite (blue asbestos), anthophyllite, tremolite, and actinolite. Chrysotile, tremolite, and crocidolite are responsible for the vast majority of pleuropulmonary disease, the form and severity of which vary with the different fiber types. Crocidolite and, to a lesser

extent, amosite are considered the most dangerous because of their carcinogenic potential.[410] Tremolite is a contaminant in most chrysotile mines and has been the subject of some debate concerning its pathogenicity;[411] however, most experts now agree that the substance can cause disease identical to that of the other forms of asbestos.[411–413] Anthophyllite was mined and used in Finland until 1970, but commercial production has now ceased, and it is usually identified in small amounts in lung fiber analyses.

Chrysotile fibers are curved, whereas the amphiboles are straight (Fig. 60–29). These physical properties as well as chemical differences are responsible for the varying uses of asbestos; for example, chrysotile fibers are particularly suitable for textile manufacture because they are long and pliable, whereas crocidolite and amosite are of greater value for marine insulation because they are more acid resistant. Different physiochemical properties between chrysotile and the amphiboles are also likely to have an influence on deposition patterns and clearance in the lung and on pathogenicity.

Epidemiology

The use of asbestos in industry increased enormously during the first three quarters of the twentieth century; world production jumped from 500 tons in 1900 to 3 million tons in 1968[415] to an estimated 6 million tons in 1981.[416] As a result of concerns about asbestos exposure and cancer, more recent production has stabilized at about 4 million tons per year.[409] Although recognition of the harmful effects of asbestos exposure has resulted in better control of dust levels and an overall decrease in total exposure, the potential for the development of serious disease still exists.[417–421] For example, it has been estimated that in the United States 8 to 9 million people have had occupational exposure to asbestos[422, 423] and that such exposure will eventually result in 300,000 deaths.[424]

The major producers of asbestos are Russia, Canada (principally Quebec), Zimbabwe, and South Africa; virtually all amosite and crocidolite is produced in South Africa, and most chrysotile comes from Russia and Quebec. Chrysotile is the most important form commercially, accounting for about 95% of the total asbestos marketed in the United States and elsewhere, mainly as asbestos cement.[409] In mining and milling, exposure occurs predominantly to only one type of fiber, although small amounts of other types may be present, even in commercially "pure" preparations.[425] By contrast, mixtures of fibers are commonly employed in construction and in the manufacture of textiles, and exposure to several fiber types is routine in these situations.

The three major sources of exposure to asbestos are (1) the primary occupations of asbestos mining and its processing in a mill, (2) numerous secondary occupations involving its use in a variety of industrial and commercial products, and (3) nonoccupational (environmental or paraoc-

Figure 60–29. Types of Asbestos Fiber. Electron microscopic views of four different types of asbestos fiber show the amphiboles (crocidolite, amosite, and anthophyllite) to be straight and chrysotile to be distinctly curved. (From Timbrell B: Physical factors as etiologic mechanisms. IARC Sci Pub 8: 295, 1973.)

cupational) exposure to contaminated air. In some individuals, such as those living adjacent to asbestos mines, such nonoccupational exposure can be substantial; however, in the majority, it is minimal and is evidenced only by the presence of asbestos fibers in digests of lung tissue.

The secondary uses of asbestos are numerous (Table 60–1). The most important are in the construction industry, in which asbestos is extensively incorporated in cement, pipes, tiles, mouldings, and paneling; shipbuilding and repair;[426–428] boiler making and repair;[429] railroad occupations;[430] the manufacture of textiles and plastics;[431] the manufacture and repair of gaskets and brake linings (although most insulation and friction materials are now made with nonasbestos fibers[409]); dentistry (affecting both dentists and dental technicians);[432] and the jewelry industry.[433] Although the risk of asbestos exposure applies during the manufacturing process, it is greater during demolition, such as occurs in construction[418] and elevator servicing.[434] Although the fiber is generally assumed to be well bound and harmless once it is incorporated into manufactured products,[435] reports of significant levels of airborne asbestos in buildings with deteriorating insulation leaves even this assumption in doubt.[436, 437] Such potential exposure may be the cause of the increased prevalence of asbestos-related disease that has been reported in groups such as public school custodians.[438]

Environmental exposure to asbestos dust also occurs in individuals not directly involved in asbestos-related occupations.[439] The wide distribution of this mineral throughout the world is indicated by the frequency with which asbestos bodies can be found in routine autopsies, the prevalence ranging from 1% in rural Italy[440] to as high as 60% in New York City.[441] In urban areas such as Miami,[442] Glasgow,[441] London,[443] Pittsburgh,[444] Melbourne,[445] and Montreal,[446] the prevalence has ranged from 25% to 50%.

Although the identification of asbestos bodies in the lungs in routine autopsies indicates that exposure to the mineral is almost universal, there is no evidence that this is associated with a significant risk for the development of pleuropulmonary disease in most individuals.[447, 448] However, there is a substantial amount of evidence that individuals who live in the vicinity of a mine, mill, or factory that engenders heavy asbestos dust pollution have a greater incidence of pleural plaques and mesothelioma.[449–452] In fact, these abnormalities can develop in persons whose only expo-

Table 60–1. OCCUPATIONS AT RISK FOR ASBESTOS EXPOSURE: MINING, MILLING, MANUFACTURING, AND SECONDARY USES

PROCESS	PRODUCTS MADE OR USED	JOBS POTENTIALLY AT RISK
Production		
Mining		Rock mining, loading, trucking
Milling		Crushing, milling
Handling		Transport workers, dockers, loaders, those who unpack jute sacks (replaced with sacks that do not permit fibers to escape)
Primary Uses		
Spray insulation	Spray of fiber mixed with oil	Spray insulators (construction, shipbuilding)
Filler and grouting		
Manufacturing of textiles	Cloth, curtains, lagging, protective clothing, mailbags, padding, conveyor belts	Blending, carding, spinning, twisting, winding, braiding, weaving, slurry mixing, laminating, molding, drying
Manufacturing of cement products	Sheets, pipes, roofing shingles, gutters, ventilation shafts, flower pots	Blending, slurry preparation, rolling, pressing, pipe cutting
Manufacturing of paper products	Millboard, roofing felt, fine-quality electrical papers, flooring felt, fillers	
Manufacturing of friction materials	Automotive products: gaskets, clutch plates, brake linings	
Manufacturing of insulation products	Pipe and boiler insulation, bulkhead linings for ships	
Applications		
Construction		
New construction	Boards and tiles; putties, caulk, paints, joint fillers; cement products (tiles, pipes, siding, shingles)	Direct: carpenters, laggers, painters, tile layers, insulation workers, sheet metal and heating equipment workers, masons Indirectly: all other workers on construction sites, such as plumbers, welders, electricians
Repair, demolition		Demolition workers for all of these
Shipbuilding		
Construction	Insulation materials (boards, mattresses, cloth) for engines, hull, decks, lagging of ventilation and water pipes, cables	Laggers, refitters, strippers, steam fitters, sailmakers, joiners, shipwrights, engine fitters, masons, painters, welders, caulkers
Repair, refits	Insulation materials, as described for Construction	Directly: all above jobs on refits, dry dock, and other repair operations Indirectly: maintenance fitters and repairers, electricians, plumbers, welders, carpenters
Automotive industry		
Manufacture	Gaskets, brake linings, undercoating	Installation of brake linings, gaskets, and so on
Repair	Gaskets, brake linings, undercoating	Service people, brake repairers, body repairers, auto mechanics

Modified from Becklake MR: Am Rev Respir Dis 114:187, 1976.

sure is the repeated handling of the clothes of asbestos workers.[453–456] In addition, a particularly high prevalence of nonoccupational asbestos-related disease has been reported in some areas of Corsica[28] (where houses have been built on asbestos surface deposits) and from the Metsovo area of northwest Greece[457, 458] and isolated villages in Turkey[434, 459–461] (where the soil, which contains tremolite, has been used as a whitewash for buildings); although the manifestations of disease in these situations have been largely pleural—many of the inhabitants have pleural plaques and some mesothelioma—the possibility of an association with pulmonary carcinoma has also been raised.[462]

In clinical practice, a history of environmental or paraoccupational asbestos exposure may not be readily apparent from a cursory inquiry because the exposure may have occurred many years before the recognition of disease and may have been of short duration. An example of how remote nonoccupational exposure may be is illustrated by the story of two brothers aged 27 and 33 years who presented with chest wall and diaphragmatic pleural calcification and whose only exposure was playing in childhood in the cellar of their home, which was also used by their father in a muffler repair business.[454] Although disease caused by asbestos exposure, particularly mesothelioma, has been well described in workers who manufacture friction materials, such as brake and clutch linings,[463] the fear that there may be significant environmental contamination by asbestos dust from automobile brakes has been eliminated by studies showing that the high heat of friction on application of brakes converts asbestos to an inert nonfibrous silicate known as fosterite.[285, 464]

Pathogenesis

The pathogenesis of asbestos-related pleuropulmonary disease is complex and incompletely understood.[465, 466] The toxicity of the mineral itself appears to be related to its fibrous nature because pulverized asbestos does not cause disease.[409] Fiber dose, dimension, and durability may all influence both fibrogenicity and carcinogenicity, with longer, thinner, more durable fibers being the most biologically important.[465] Factors related to the host, including pulmonary clearance and immunologic status, and the presence of other noxious substances, such as cigarette smoke, are also undoubtedly important in determining the nature and severity of the final reaction to inhaled fibers. This section briefly outlines the factors involved in the development of asbestosis; those related to carcinogenesis of the lung and pleura are discussed on pages 1074 and 2810.

The development of asbestosis depends on the intensity and duration of exposure to asbestos fibers. Exposure has usually been accepted as a surrogate for dose in determining dose-response relationships for asbestos-related diseases; however, determinations of lung burden of asbestos fiber have enhanced the appreciation of the biology and epidemiology of these disorders.[467] It is intuitively apparent that the quantity of fiber retained in the lung is a function of both the amount of fiber that is inhaled and the amount that is subsequently cleared; both are important determinants of disease. For example, the results of an autopsy analysis of a group of Quebec chrysotile miners and millers suggest that the pathogenesis of both mesothelioma and asbestosis is linked to tremolite, a contaminant of chrysotile that is more rapidly cleared by the lung.[468] In this study, there appeared to be no correlation between the severity of pulmonary fibrosis and total fiber length, surface area, or mass.[468, 469] The same authors performed a similar study of a group of shipyard workers from the Pacific Northwest, who had been exposed to both chrysotile and amosite fibers.[470] In this group, the concentration of lung amosite, the major residual fiber, most closely correlated with asbestosis. Although these investigations have included only small numbers of control subjects (exposed workers who did not have disease), studies in a sheep model suggest that the development of disease is linked to fiber retention.[471] Although dose-response relationships exist for all pleuropulmonary manifestations of asbestos exposure, the heaviest fiber burdens are associated with asbestosis.[467, 472–474]

Although the majority of inhaled asbestos is transported out of the lung via the mucociliary escalator,[475] a variable proportion enters the interstitium, the amount depending on the efficiency of fiber clearance and the asbestos dose itself. Passage from the air-space lumen to the interstitium may be accomplished by transport within macrophages, by direct penetration across the epithelium (either within or between epithelial cells),[475] or by the organization of an intraluminal exudate after epithelial injury.[476] The initial inflammatory reaction to retained fibers is an accumulation of macrophages, particularly at transitional airway bifurcations and to a lesser extent in alveoli.[93, 409] This accumulation occurs both by recruitment of peripheral blood monocytes and by replication of macrophages at the site of fiber deposition.[477] Activated complement may be the initial chemoattractant.[478] It is also likely that alveolar interstitial macrophages increase in number and secrete potentially harmful cytokines after asbestos transfer across the epithelium.[479] Evidence of airway epithelial injury (such as increased incorporation of tritiated thymidine) can be seen as soon as 24 hours after fiber inhalation in experimental animals.[480] Such epithelial damage may facilitate the passage of fibers from the air spaces into the interstitial tissue, a process that is undoubtedly important in the development of fibrosis.

Animal and human studies have shown that the activated macrophages that accumulate at the sites of asbestos deposition secrete a variety of proinflammatory and profibrotic cytokines—including fibronectin, PDGF, IGF-1, fibroblast growth factor, IL-1β and IL-6, TNF-α, granulocyte macrophage colony-stimulating factor, and neutrophil chemotactic factor—and inflammatory mediators such as leukotriene B_4 and prostaglandin E_2.[93, 409, 482–486] These substances are clearly important as mediators of the ensuing disease. For example, in the sheep model of asbestosis, fibronectin, neutrophil chemotactic factors, and fibroblast growth factors are required both to initiate and to sustain fibrosis.[93] Persistent BAL neutrophilia in asbestos-exposed men has also been associated with progressive deterioration in lung function,[487–489] the presence of crackles on physical examination,[490, 491] and abnormal gas exchange.[491] Higher concentrations of fibronectin and PGE_2 released from cultured alveolar macrophages from asbestos-exposed workers are associated with restrictive lung function, and a neutrophilic and eosinophilic alveolitis is seen in workers who have asbestosis, independent of cigarette smoking.[485, 491] As is the case for the finding of BAL neutrophilia, increased BAL eosinophils

and fibronectin also predict worsening lung function with time.[489]

Asbestos-related tissue damage may occur by several mechanisms, one of the most important being direct damage by free radicals and other reactive oxygen species.[493–495] Endothelial injury produced by these substances may lead to the elaboration of prostacyclin, resulting in increased vascular permeability and other manifestations of inflammation.[496] The observation that genes involved in antioxidant defense are up-regulated in rats exposed to asbestos fiber is additional evidence that oxidants have a pathogenetic role.[497] In the sheep model of asbestosis, alveolar macrophages also release plasminogen activator, a protease that can cause tissue destruction, early in the course of disease.[498] Patients who have asbestosis demonstrate increased procoagulant activity in BAL fluid, which likely derives from both endothelial cells and alveolar macrophages.[499] This imbalance in the coagulation cascade might account for the enhanced fibrin deposition seen pathologically and may play a role in development of fibrosis. Deficiency of the enzyme glutathione-S-transferase does not appear to be related to tissue damage.[500]

Not everyone exposed to heavy concentrations of asbestos develops asbestosis; in fact, the dose-response relationship is weaker in this condition than in pneumoconioses such as CWP. This observation has raised the possibility that other extrinsic agents or intrinsic host factors may be important in the pathogenesis of disease. The most extensively studied extrinsic agent has been tobacco smoke. There is good epidemiologic evidence that cigarette smoking is associated with an increase in the prevalence of radiographically detectable small irregular opacities compatible with asbestosis in asbestos-exposed populations.[501, 502, 504–508] The mechanism behind this association is unclear. Animal models of asbestosis suggest that it may be related to enhanced retention of short fibers[509–511] (although the results of some studies have suggested that longer fibers are more fibrogenic than shorter ones[512–514]). Cigarette smoking also increases the number of macrophages and neutrophils in BAL fluid of patients who have asbestosis,[515] augments the release of reactive oxygen species and of the profibrotic cytokine TNF from alveolar macrophages,[493, 516] and enhances fiber transport across the airway epithelium.[517, 518] There is evidence that asbestos increases the levels of Clara cell protein (CC16) and surfactant-associated protein (SP-A) in distal air spaces;[519] by inhibiting phospholipase A_2, these molecules can potentially have an effect on local inflammatory and profibrotic events. However, because levels of CC-16 are reduced in the BAL fluid of asbestos-exposed smokers compared with asbestos-exposed nonsmokers, the importance of this effect in enhancing cigarette smoke-asbestos interaction is unclear. Lastly, a greatly enhanced asbestos-fiber burden has been demonstrated in the airways of asbestos workers who smoke compared with similarly exposed nonsmokers.[520] Any or all of these effects may be related to the the development of tissue damage and fibrosis.

Intrinsic host factors that might be important in determining individual susceptibility to the harmful effects of asbestos include the efficiency of alveolar and tracheobronchial clearance, variation in underlying lung structure,[521] and immunologic status. The last-named has been the most thoroughly studied, both in animal models and in affected workers. Some patients who have asbestos exposure demonstrate a predominantly lymphocytic alveolitis,[522] a form of inflammation that seems to protect against the development of pulmonary fibrosis[488, 522] but to promote the development of pleural plaques.[523] This observation has been supported by experiments in mice with severe combined immunodeficiency, who have been shown to develop a more severe inflammatory and fibrotic response to asbestos than control animals.[524] This protective effect may be related to the elaboration of γ-interferon, which has antifibrotic properties.[522, 525] There is also evidence that the presence of a lymphocytic alveolitis may be associated with a decreased risk for the development of mesothelioma.[526] In a large study of asbestos-exposed workers, most of whom did not have asbestosis, an increased helper-to-suppressor T cell ratio was found in peripheral blood associated with an increase in suppressor CD8 cells in BAL fluid, suggesting a redistribution of these cells from blood to lung.[527] Workers who had pleural plaques had an increased helper-to-suppressor ratio of T lymphocytes in BAL fluid; similar changes were seen in the peripheral blood of the few workers who had asbestosis.

As in some other pneumoconioses, evidence of altered immunologic activity is not uncommon in asbestos-exposed individuals. Circulating rheumatoid and antinuclear factors have been identified in 25% to 30% of asbestos workers who have abnormal chest radiographs, albeit in titers considerably lower than those usually identified in connective tissue diseases.[528] In workers exposed to asbestos, some investigators have found hypergammaglobulinemia, a variety of additional autoantibodies, and even immune complexes.[529–531] Although such B-cell hyperactivity appears to correlate with radiographic progression of asbestosis,[531] there is as yet no clear-cut evidence that it is directly involved in the pathogenesis of the disease.[529, 530] In contrast to B-cell function, cell-mediated immunity, as measured by either delayed hypersensitivity skin tests or *in vitro* methods, is reduced in patients who have relatively advanced asbestosis;[532–534] the results of one investigation suggest that this abnormality may antedate the radiographic appearance of fibrosis.[534]

Although the studies just cited raise the possibility of an immunologic factor in the pathogenesis of asbestosis, not all investigators have confirmed this. For example, in an investigation of anthophyllite asbestos workers in Finland, the prevalence of rheumatoid factor was found to be similar to that in healthy control groups.[535] In another study of long-term asbestos workers from Quebec (more than half of whom had asbestosis) and a reference population of local residents, no significant difference in the frequency of HLA phenotypes was found between the two groups.[536] These results have been confirmed in more recent studies.[537, 538]

Pathologic Characteristics

Pathologic abnormalities in the chest caused by asbestos inhalation can occur in the pleura, lung parenchyma, airways, and lymph nodes. Pleural disease is the most common and usually takes the form of parietal pleural plaques; localized visceral pleural fibrosis, more or less diffuse pleural fibrosis, and mesothelioma (each of which can be associated with pleural effusion) also occur. Pulmonary manifestations include diffuse interstitial fibrosis (asbestosis), round atelectasis, peribronchiolar fibrosis, and pulmonary carcinoma.

In addition to these pathologic abnormalities, evidence of asbestos exposure can also be seen in tissue sections by the identification of iron-coated asbestos fibers. These asbestos bodies are most often found in lung parenchyma but also occur in airway walls and intrathoracic lymph nodes. The discovery of such bodies in tissue sections, pulmonary secretions, or BAL fluid does not by itself signify the presence of asbestos-related pleuropulmonary disease; however, it strongly suggests that the patient has been exposed to a significant quantity of the mineral, usually in an occupational setting.

Pleural Manifestations

Pleural Plaques

As indicated, pleural plaques are the most common form of asbestos-related pleuropulmonary disease and are frequently unassociated with any other pathologic abnormality.[539-542] Grossly, they typically consist of well-demarcated, pearly white foci of hard fibrous tissue, 2 to 5 mm thick and several centimeters in diameter.[543] They can have a smooth or nodular surface and be round, elliptical, or irregular in shape (Fig. 60–30).[544] Foci of calcification are not uncommon and are occasionally extensive. Characteristically, the plaques are located on the parietal pleura overlying the ribs and on the dome of a hemidiaphragm. They are generally absent from the apices, costophrenic angles, and anterior chest wall and are almost always bilateral. Although plaques identical to those on the parietal pleura can also occur on the visceral surface, they are distinctly uncommon in this location; in our experience, such plaques are small and tend to be located in the interlobar fissures. Plaques can also be found on the peritoneal surface.[545]

Histologically, plaques are composed of dense bands of collagen often arranged in a "basket-weave" configuration (Fig. 60–31); inflammation, characterized by lymphocytes, is usually mild and focal.[541, 543, 544] Rarely, the fibrous tissue has an active (fibroblastic) appearance, suggesting a stage in plaque development (*see* Fig. 60–31); such "presumptive" plaques are seen most often in biopsy specimens taken during the investigation of benign asbestos effusion. Asbestos bodies are invariably absent in the plaques, although uncoated fibers may be demonstrated when the tissue is dissolved or ashed and examined under polarized light or by electron microscopy.[539, 546, 547]

Parietal pleural plaques are common, the incidence in consecutive routine autopsies ranging from about 5% to 10%.[541, 543] In most cases, there is evidence of prior asbestos exposure, as indicated by either an appropriate occupational history or the presence of a substantial number of asbestos bodies or uncoated asbestos fibers within the lungs.[540, 541, 548-550] In some patients, however, asbestos bodies are not demonstrable, and an exposure history is lacking;[539, 540, 551] as a result, plaques cannot be regarded as absolute evidence of an asbestos etiology, although they are certainly highly suggestive. Whether non–asbestos-related plaques are caused by trauma, infection, or inhalation of other mineral fibers usually cannot be established.

The pathogenesis of pleural plaques is unclear, and several mechanical, chemical, and immunologic mechanisms have been invoked to explain their formation.[459] It is known that inhaled asbestos fibers can be deposited in the periphery of the lung, from which they can be transported to the pleura. Mesothelial cells are able to phagocytose foreign particles, including asbestos, and have been shown to secrete the fibroblast chemoattractant, fibronectin.[552] Direct stimulation of pleural connective tissue cells by the asbestos fibers is also theoretically possible. Why the plaques preferentially develop in the parietal pleura is not apparent.

Focal Visceral Pleural Fibrosis

Relatively discrete foci of visceral pleural fibrosis morphologically distinct from pleural plaques are also not uncommon after asbestos exposure. They are most frequently located on the lateral aspect of a lower lobe and consist of ill-defined areas of fibrous tissue that usually measure only 0.5 to 1 mm in thickness. In fact, the fibrosis may be manifested by no more than a creamy white "cloudiness" that is barely perceptible as thickening (Fig. 60–32). More advanced lesions may appear to radiate from a central focus of relatively thicker fibrous tissue (*see* Fig. 60–32). The underlying lung may be normal or may show partial or complete collapse (round atelectasis; *see* farther on). Histologically, the lesion consists of mature fibrous tissue that contains a variable number of chronic inflammatory cells. Unless associated with round atelectasis or located in a fissure, the abnormality is unlikely to be detected on chest radiographs or CT.

Diffuse Pleural Fibrosis

In contrast to the relatively discrete foci of visceral and parietal pleural fibrosis described previously, some patients show more diffuse pleural thickening.[423] Although this thickening can be restricted to either the parietal[423] or visceral[553] pleura, it usually involves both and is accompanied by interpleural adhesions. The fibrosis can extend to adjacent interlobar fissures and interlobular septa[423] and even into the mediastinum;[554] however, because the lung parenchyma itself is not affected, asbestosis is by definition not present. Histologically, the lesions are composed of mature collagen and a variable number of chronic inflammatory cells. Acute fibrinous pleuritis[423] and interstitial fibrosis limited to the adjacent pulmonary parenchyma[553] are sometimes present.

It is not clear whether this form of pleural disease represents an exaggeration of one or both of the other two forms of fibrosis or is a pathogenetically separate process. In one study of seven patients who had diffuse pleural fibrosis, one or more episodes of prior pleural effusion were identified, suggesting that organization of the effusion might have been responsible for the chronic changes.[423] The presence of numerous inflammatory cells within the fibrous tissue in some cases has also raised the possibility of an immunologic contribution to the pathogenesis.[554]

Pleural Effusion

Histologic examination of the pleura from patients who have benign asbestos effusion may show fibrosis and nonspecific chronic inflammation;[555, 556] however, in our experience, an organizing fibrinous exudate is more common. In many cases, the fibrosis is a microscopic finding only, although in

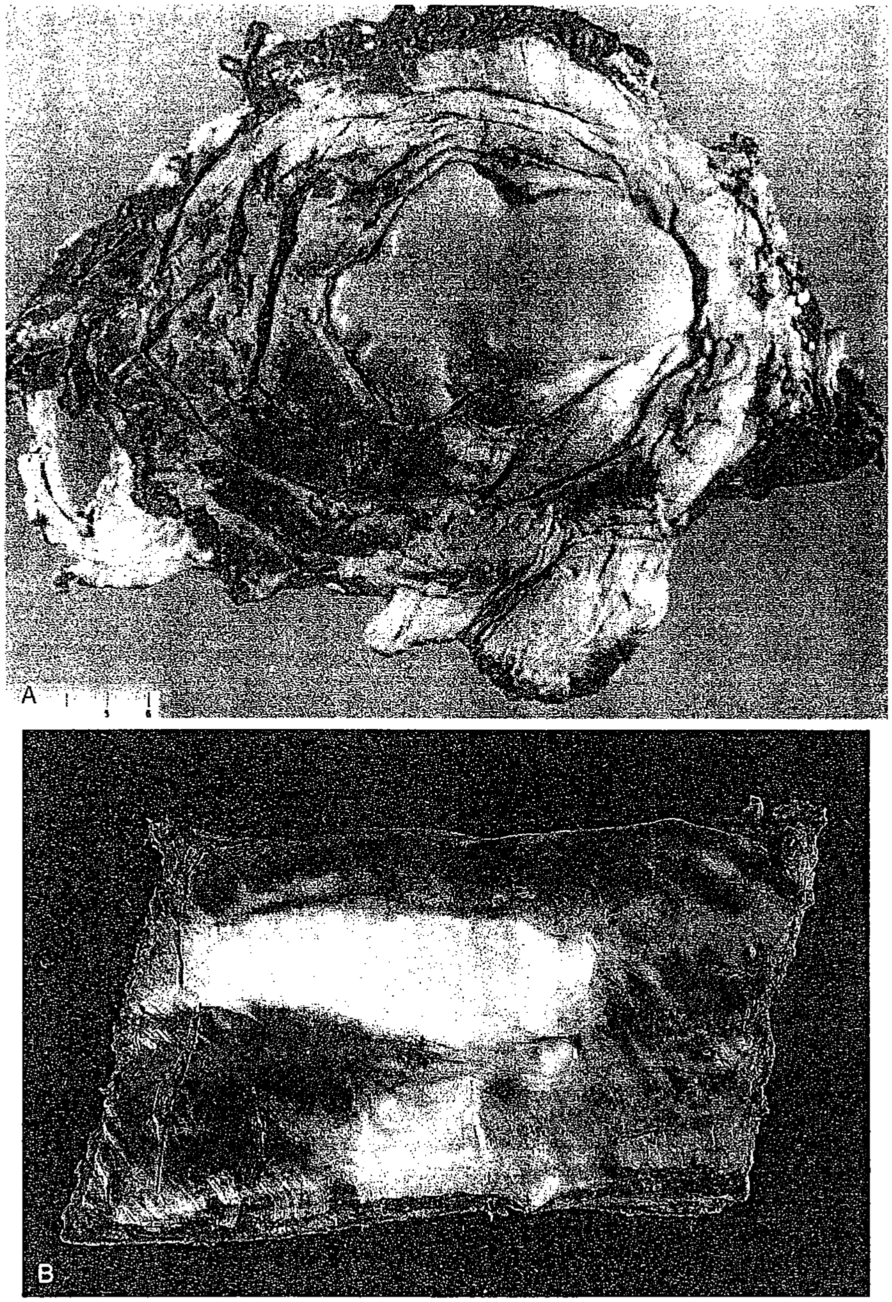

Figure 60–30. Parietal Pleural Plaques: Gross Appearance. A specimen of a hemidiaphragm *(A)* shows a smooth, pearly white, well-circumscribed area of fibrosis on the tendinous portion. A segment of two ribs *(B)* shows similar foci of fibrosis, one of which is elongated and roughly parallel to the long axis of the rib.

some it has also been associated with grossly identifiable diffuse pleural fibrosis.[423] Mesothelial hyperplasia may be present and must be distinguished from mesothelioma. As with other forms of asbestos-related pleural disease, the pathogenesis of nonneoplastic effusion is unclear. On the basis of experimental studies in rabbits, it has been suggested that interaction between asbestos fibers and pleural tissue results in the release of non–complement-related chemotactic factors that cause the effusion.[557] This hypothesis has been supported by the results of a study of rabbit mesothelial cells in which incubation with asbestos fibers was followed by the release of a substance that possessed chemotactic activity for neutrophils.[558]

Mesothelioma

There is no doubt of the association between asbestos exposure and the development of mesothelioma. The pathologic features and pathogenesis of this tumor are discussed in greater detail on page 2810.

Pulmonary Manifestations

Asbestos Body

Asbestos bodies are seen commonly in tissue sections in association with asbestos pleuropulmonary disease. They consist of a central transparent asbestos fiber surrounded by

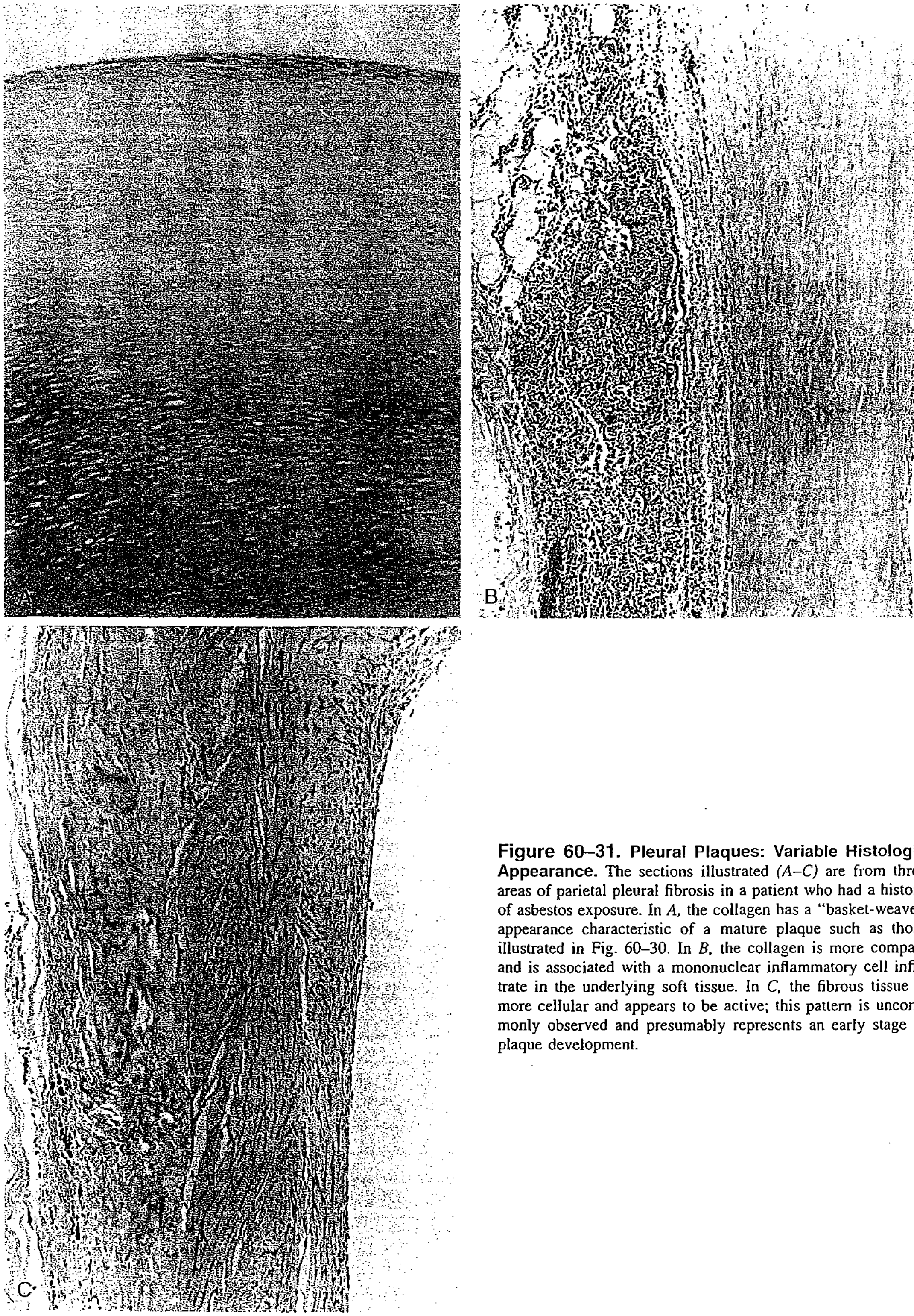

Figure 60–31. Pleural Plaques: Variable Histologic Appearance. The sections illustrated *(A–C)* are from three areas of parietal pleural fibrosis in a patient who had a history of asbestos exposure. In *A*, the collagen has a "basket-weave" appearance characteristic of a mature plaque such as those illustrated in Fig. 60–30. In *B*, the collagen is more compact and is associated with a mononuclear inflammatory cell infiltrate in the underlying soft tissue. In *C*, the fibrous tissue is more cellular and appears to be active; this pattern is uncommonly observed and presumably represents an early stage in plaque development.

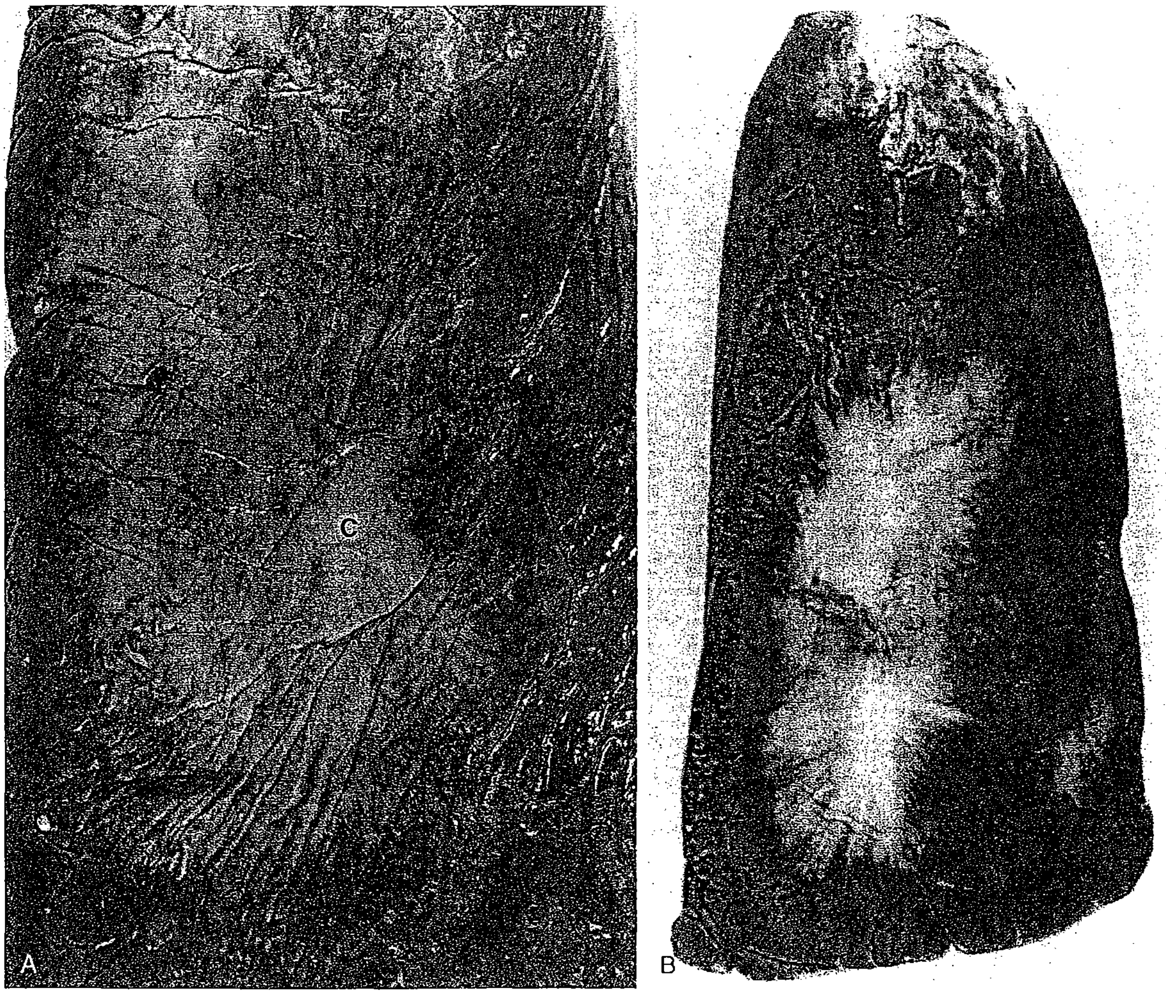

Figure 60–32. Localized Visceral Pleural Fibrosis Secondary to Asbestos Exposure. A magnified view of the lateral aspect of a lower lobe *(A)* shows a large portion of the pleura to have a creamy white appearance (compare with the normal pleura at the edge of the specimen). Except for the central region (C), the actual thickening of the pleura is barely perceptible. The lateral surface of another lower lobe *(B)* shows a more obvious but still rather poorly demarcated area of fibrosis that appears to radiate from two central foci. The underlying lung was unremarkable. (A fibrinous exudate related to premortem pneumonia is evident on the superior segment.) Both patients had a history of asbestos exposure.

a variably thick coat of iron and protein (Fig. 60–33). Most bodies measure 2 to 5 μm in width and 20 to 50 μm in length; the asbestos fibers themselves usually range from 0.1 to 1.5 μm in diameter.[559] The shape is quite variable depending on the length of the asbestos fiber, the amount and pattern of deposition of the protein-iron coat, and whether the body is whole or fragmented. The coat is often segmented over the length of the fiber and sometimes forms bulbous projections at both ends, resulting in a drumstick appearance (*see* Fig. 60–33). The majority are straight, although curved and angulated forms can be seen. The core of most asbestos bodies consists of amphiboles, especially amosite and crocidolite.[559, 560] The relative paucity of chrysotile cores probably results from the tendency of this substance to dissolve and fragment into forms that are too short to form bodies.[561]

In tissue sections, asbestos bodies are usually found in macrophages and may be in the interstitial tissue or air spaces; as indicated previously, they are rarely identified in pleural plaques. They can also be present in hilar and mediastinal lymph nodes[562] and even in extrathoracic visceral organs,[563, 564] where they have been reported to cause fibrosis.[565] Their presence in airway secretions, such as sputum, has been well documented in individuals who have occupational exposure,[566–568] and they are sometimes seen in specimens obtained by transthoracic needle aspiration.[569] They are usually not evident in specimens of pleural fluid.[568] Staining for iron can be helpful for identification, especially when few bodies are present.

Light microscopic examination of fluid obtained by BAL has also been employed as a means of identifying asbestos bodies. Using this technique, evidence of previous exposure to asbestos can be readily documented,[570] the number of asbestos bodies found in the fluid specimens generally correlating with the number in lung tissue sections.[571, 572] Although significant exposure has been considered to be excluded by either the complete absence of asbestos bodies[490, 573] or the presence of a small number,[574] there are some

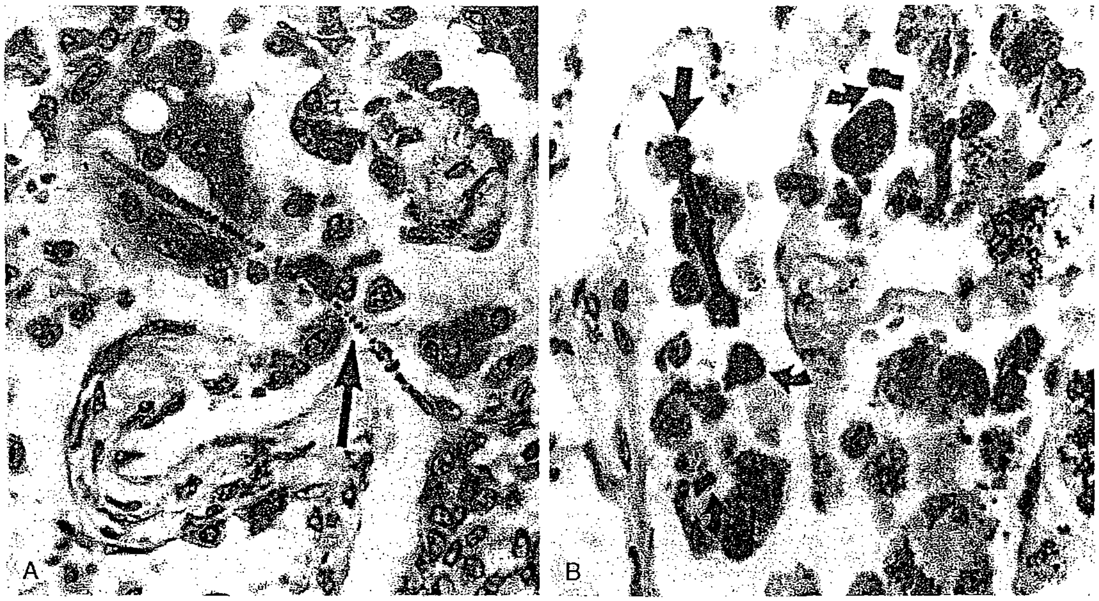

Figure 60–33. Asbestos Bodies. A histologic section *(A)* reveals a typical asbestos body consisting of a slightly curved, elongated structure with a finely beaded iron-protein coat. The asbestos fiber itself can be identified as a thin line in the center of the coat near one end of the body *(arrow)*. In another section *(B)*, other asbestos bodies show a more prominent iron-protein coat obscuring the enclosed asbestos fiber; some bodies appear to be fragmented *(curved arrows)*: A characteristic drumstick form is taken by one *(straight arrow)*. (*A* and *B*, ×400.)

exposed workers whose fluid contains no bodies.[575] In one study, the highest asbestos body counts were found in patients who had clinical evidence of asbestosis;[574] however, in two others, quantitative analysis did not serve to distinguish asbestos workers who had disease from those who did not,[490] and no association of body number with radiographic or functional abnormalities could be documented.[575]

It is widely believed that asbestos bodies are formed within an alveolar macrophage by deposition of a glycoprotein matrix and iron around a phagocytosed asbestos fiber.[559, 576] There is some evidence, however, that iron-protein deposition may also take place in the extracellular tissue adjacent to the macrophage.[577] The source of the iron may be red blood cells released as a result of asbestos-related tissue injury or circulating iron stores.[559] The encasement of foreign material by an iron-glycoprotein coat is not unique to asbestos; it has been shown to occur in experimental animals around fiberglass or synthetic aluminum silicate particles[578] and in humans around a variety of particles, including talc, mica, carbon (*see* Figs. 60–22 and 60–65), diatomaceous earth, rutile (a form of titanium dioxide), fly ash, zeolite, silicon carbide, and even iron itself.[579–582] With the exception of zeolite, such nonasbestos ferruginous bodies can usually be distinguished from true asbestos bodies by the appearance of the fiber core, which is thin and translucent with asbestos and black or colored and often thick with other particles.[579, 580]

Although for practical reasons, asbestos bodies are most often identified in tissue sections, their true number is best estimated by examining concentrates of digested lung tissue;[583] for example, it has been estimated that microscopic examination of 30 to 40 fields at a magnification of 400 would be necessary to find a single asbestos body in a tissue section from lung that contains 5,000 bodies per gram.[584] Because of its sensitivity, the use of a digestion technique permits identification of asbestos bodies in virtually all individuals in the general population,[585, 586] whereas microscopic examination of tissue sections reveals them only rarely in the absence of occupational exposure.

Attempts have been made to correlate the number of asbestos bodies seen in tissue sections with the number identified in tissue digests. In one study of six individuals who had asbestosis or asbestos-related neoplasia, an average of two asbestos bodies on 2 × 2 cm iron-stained tissue sections 5 μm thick was found to be equivalent to approximately 200 asbestos bodies per gram of wet-fixed lung tissue.[587] In another investigation of seven patients who had asbestosis, one asbestos body in a 4-μm tissue section of average area 3.25 cm^2 was found to be equivalent to 1,000 per gram of wet tissue.[588] A mathematical model has been developed that has been claimed to be even more accurate in predicting total lung asbestos body concentration from the number of asbestos bodies in tissue sections.[584] Even in the presence of fibrosis and a high asbestos fiber burden, however, asbestos bodies may be scarce or absent in tissue sections of some subjects.[589]

Although the presence of a substantial number of asbestos bodies in digested lung samples examined by ordinary light or phase contrast microscopy is a reliable indicator of significant asbestos exposure, it is clear that the absolute number of asbestos *bodies* identified by these means is a gross underestimation of the total number of uncoated asbestos *fibers* as determined by electron microscopic examination.[559, 585, 590] Thus, the ratio of uncoated to coated fibers in lung digests ranges from approximately 7:1 to 5,000:1 in different series.[585] Because it is likely that the fibers rather than the coated asbestos bodies are involved in the pathogenesis of disease, this discrepancy in number is clearly important. In individuals who do not have occupational exposure, most uncoated fibers are short (< 5 μm in length) and

consist of chrysotile or noncommercial amphiboles, such as tremolite and anthophyllite.[591]

The number of asbestos bodies and fibers per gram of digested lung tissue is roughly proportional to both the presence and severity of disease and the degree of occupational exposure.[559, 585, 586, 592] Thus, individuals who have well-documented high exposure generally have a 20-fold to 100-fold increase in the total number of fibers within the lung compared to controls;[585] individuals who have asbestosis or mesothelioma often have a 100-fold to 1,000-fold relative increase.[585] As might be expected, individuals who have environmental (nonoccupational) asbestos exposure generally have levels between those of individuals who have an occupational history and those of the general population.[593] Analysis of specific fibers may be helpful in distinguishing background exposure to asbestos from that related to occupational exposure, the finding of chrysotile or tremolite fibers longer than 8 μm being highly suggestive of the latter.[594]

Asbestosis

Asbestosis can be defined as diffuse pulmonary parenchymal interstitial fibrosis secondary to the inhalation of asbestos fibers. The condition is usually associated with a history of prolonged occupational exposure to asbestos and with a large number of asbestos bodies and fibers in samples of lung tissue treated by digestion techniques.[585] Frequently, asbestos bodies are also visible in tissue sections, where they may also be present in great numbers.

Grossly, the fibrosis is most prominent in the subpleural regions, particularly of the lower lobes, and varies from a slightly coarsened appearance of the parenchyma to obvious honeycomb change (Fig. 60–34).[544, 592] As might be expected from this gross description, the microscopic appearance varies from a mild increase in interstitial collagen to complete obliteration of normal lung architecture associated with the formation of thick fibrous bands and cystic spaces (Fig. 60–35). An inflammatory cellular reaction is usually mild; if prominent, the possibility of idiopathic pulmonary fibrosis should be considered. It is important to remember that parenchymal fibrosis limited to the immediate subpleural region may represent a reaction to adjacent pleural fibrosis, rather than asbestosis; thus, to diagnose the latter condition, fibrosis should also be documented at a distance from the subpleural region when the pleura is fibrotic.

The cystic spaces formed as a result of the parenchymal fibrosis may be lined by metaplastic bronchiolar cells or by hyperplastic type II cells, the latter sometimes containing well-demarcated eosinophilic inclusions within their cytoplasm that are identical histochemically and ultrastructurally to those seen in the liver secondary to alcohol toxicity (Mallory's hyaline) (Fig. 60–36).[595, 596] (When first described, these inclusions were thought to be specifically related to injury by asbestos;[595] however, it is now apparent that they can be caused by a variety of pulmonary insults.[596] Thus, from a diagnostic point of view, their principal significance is that they not be confused with viral inclusions.) A grading system to assess the severity of interstitial fibrosis on a systematic basis has been proposed.[544]

The earliest histologic change in asbestosis is considered by some authorities to consist of fibrosis in the walls of respiratory bronchioles.[425, 544, 597] According to this view, the process begins in the most proximal of such airways and extends in time to involve membranous and other respiratory bronchioles and eventually the adjacent alveolar interstitium; as the disease progresses, greater portions of lung parenchyma are affected in a centrifugal fashion. Although there is no doubt that peribronchiolar fibrosis occurs in association with asbestos exposure (Fig. 60–37), some investigators have suggested that it may represent a process pathogenetically distinct from pulmonary parenchymal fibrosis and should thus be termed *mineral dust airway disease* rather than asbestosis.[598–601] This view is based on the observation that airway abnormalities similar to those in asbestos workers can be identified in patients who have a history of exposure to mineral dust other than asbestos,[600] implying that the airway changes represent a nonspecific reaction. The results of experimental studies in sheep have also provided evidence for two distinct pulmonary reactions, one related to small airways and the other to the parenchymal interstitium.[598] Whatever its relationship to interstitial fibrosis, the peri-

Figure 60–34. Diffuse Pleural Fibrosis and Asbestosis. A slice through the midportion of a lower lobe shows marked pleural thickening and parenchymal interstitial fibrosis. The pleural lesion consists of fibrous tissue, which extends over most of the costal surface; although focally it appears to be related predominantly to the parietal pleura, interpleural adhesions are present in many areas. The pulmonary fibrosis is most evident in the subpleural region and has a distinctive honeycomb appearance.

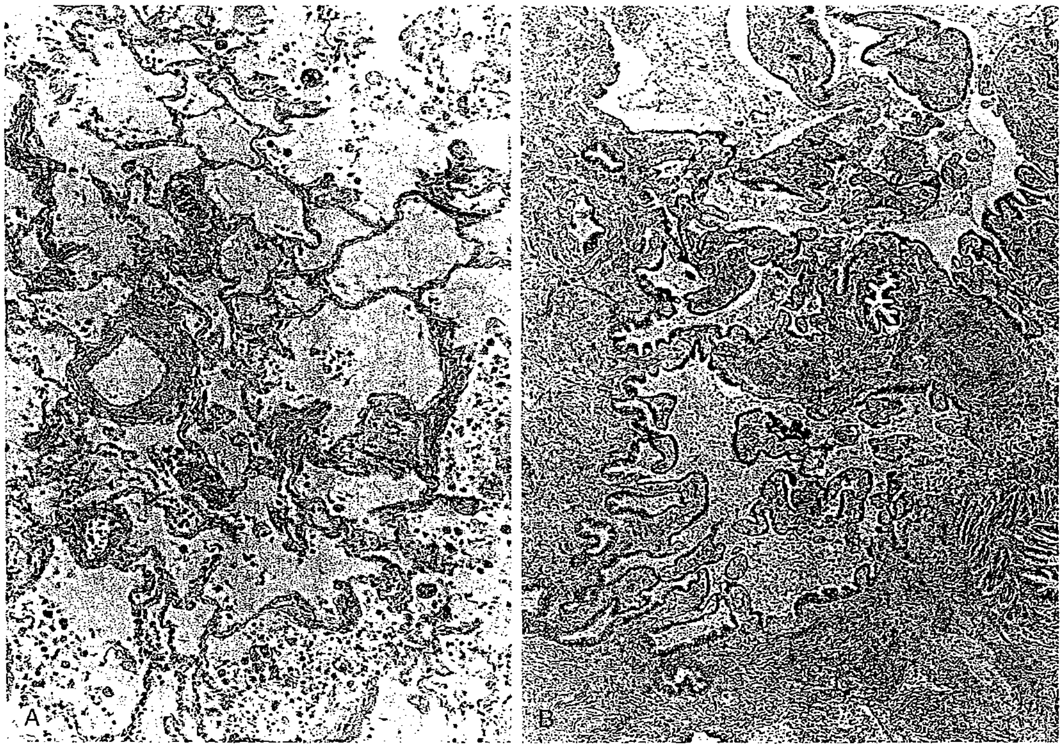

Figure 60–35. Asbestosis: Histologic Appearance. Sections show mild *(A)* and severe *(B)* interstitial fibrosis. In *A*, collagen is present in the walls of several transitional airways and alveolar septa. In *B*, there is marked distortion of lung architecture associated with the presence of broad bands of fibrous tissue and cystic spaces focally lined by metaplastic bronchiolar epithelium (corresponding to honeycomb lung). (*A*, ×100; *B*, ×30.)

bronchiolar and alveolar duct fibrosis seems likely to be related to the air-flow obstruction that is observed in both patients[602–606] and experimental animals.[598, 607, 608]

Round Atelectasis

Round atelectasis consists of a focus of collapsed lung parenchyma partly surrounded by thickened, invaginated pleura.[609–613] Although the area of collapse is usually only several centimeters in diameter and located in the periphery of the lung, involvement of a whole lobe can be seen.[614] The majority of cases are associated with asbestos-related visceral pleural fibrosis;[615–618] other causes, such as tuberculosis, are evident occasionally. Grossly, the atelectatic lung is poorly defined and appears to blend imperceptibly with the adjacent normal lung parenchyma (Fig. 60–38).[610] The overlying pleura is invariably fibrotic and shows one or more invaginations that may measure as much as 0.5 cm in thickness and extend several centimeters into the adjacent lung (Fig. 60–39). Pleural wrinkling and folding and a variable degree of alveolar collapse and fibrosis are seen microscopically (*see* Fig. 60–38). The pathogenesis of the disorder is discussed on page 522.

Other Forms of Pulmonary Parenchymal Disease

The histologic pattern of bronchiolitis obliterans with organizing pneumonia (BOOP) has been described in biopsy specimens from some patients whose radiographs have shown a localized opacity.[32, 619] It is not clear whether these cases represent an unusual reaction to inhaled asbestos or simply idiopathic BOOP in patients who happen to have been exposed to asbestos. Both lymphocytic interstitial pneumonitis[620] and idiopathic pulmonary fibrosis[621] have been reported in asbestos-exposed individuals. Distinction of these abnormalities from asbestosis can be difficult; histologic features that favor idiopathic pulmonary fibrosis include the presence of a prominent interstitial inflammatory reaction, a predominance of parenchymal compared to peribronchiolar fibrosis, a varied pattern with foci of apparently active disease (inflammation, fibroblastic tissue) adjacent to foci of mature interstitial fibrous tissue, and an absence of asbestos bodies. Rarely, the lungs of asbestos-exposed individuals have also been reported to show granulomatous inflammation similar to sarcoidosis;[619] again, it is unclear whether this represents an unusual reaction to asbestos or an entirely different disease process.

Pulmonary Carcinoma

As with mesothelioma, there is no doubt about the significant relationship between asbestos exposure and pulmonary carcinoma, particularly in cigarette smokers; the issue is discussed in Chapter 31 (*see* page 1074).

Radiologic Manifestations

Radiologic manifestations of asbestos-related disease are much more common in the pleura than in the paren-

Figure 60–36. Asbestosis: Type II Cell Inclusions. A highly magnified view of lung parenchyma with asbestosis shows macrophages and hyperplastic type II cells, some of which contain smudged, densely eosinophilic cytoplasmic inclusions *(arrows)*; they are similar to those seen in hepatocytes secondary to alcohol toxicity (Mallory's hyaline). (×600.)

chyma.[622–625] For example, in one study of 40 patients, only 5 had parenchymal changes; pleural plaques were the sole manifestation of disease in the other 35.[625] In another study of 56 patients, 48% showed asbestos pleural disease alone; 41%, combined pleural and parenchymal manifestations; and 11%, parenchymal changes alone.[623] Radiographic evidence of pleural abnormalities is present in the majority of patients who have asbestosis; in one investigation of 133 such patients, 88 (66%) had pleural changes, including 78 (59%) who had pleural calcification.[626] Overall, it has been estimated that there may be as many as 1.3 million people in the United States who have radiographically detectable asbestos-related pleural thickening.[422]

CT, in particular HRCT, has a higher sensitivity than chest radiography in the detection of both pleural and parenchymal abnormalities.[627–629] In a prospective analysis of 100 asbestos-exposed workers, pleural abnormalities were evident on the chest radiograph in 53 and on HRCT in 93;[628] parenchymal abnormalities consistent with asbestosis were present on the radiograph in 35 and on HRCT in 73. Asbestos-related pleural thickening can be seen in 95% to 100% of patients who have evidence of asbestosis on HRCT.[627, 628, 630]

Pleural Manifestations

Four types of radiologic abnormality occur in the pleura: focal plaque formation, diffuse thickening, calcification, and effusion. Each type may occur alone or in combination with the others.

Pleural Plaques

Radiographically, pleural plaques usually are more prominent in the lower half of the thorax and tend to follow the ribs when seen *en face*.[546, 631, 632] They may be smooth or nodular in contour and can measure up to 1 cm in thickness, although they are usually thinner (Fig. 60–40). They are seen most commonly on the domes of the diaphragm, on the posterolateral chest wall between the seventh and tenth ribs, and on the lateral chest wall between the sixth and ninth

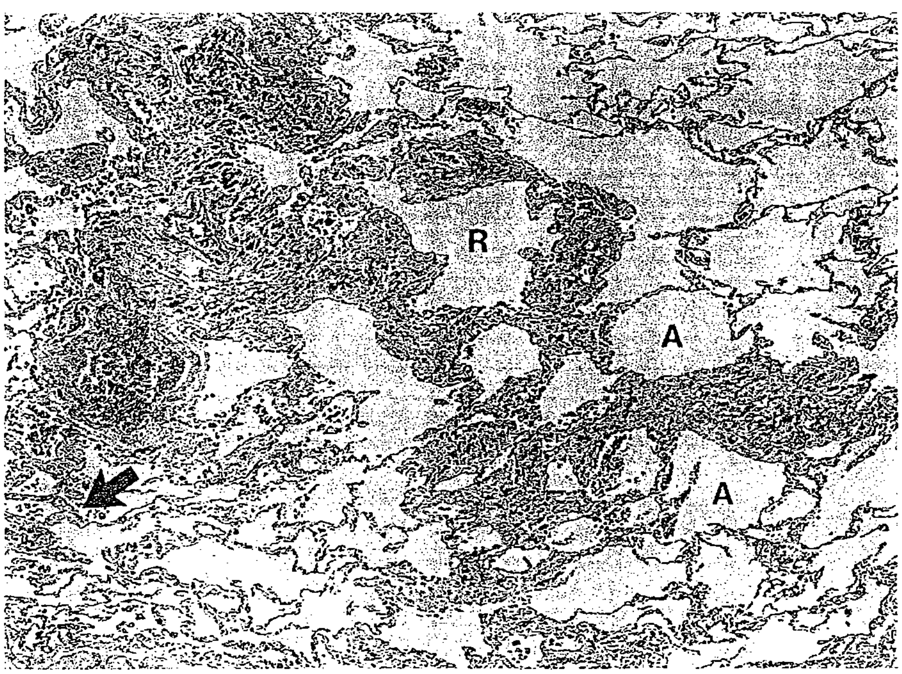

Figure 60–37. Peribronchiolar Fibrosis Associated with Asbestos Exposure. In this histologic section, the wall of a respiratory bronchiole (R) and its daughter alveolar ducts (A) are substantially thickened by fibrous tissue, pigmented macrophages, and a mild lymphocytic infiltrate. The adjacent parenchyma shows focal mild interstitial fibrosis *(arrow)*. The pattern is consistent with early asbestosis (asbestos bodies were easily identified in the fibrotic areas and the adjacent lung parenchyma). The patient was a 55-year-old man employed as an insulator. (×40.)

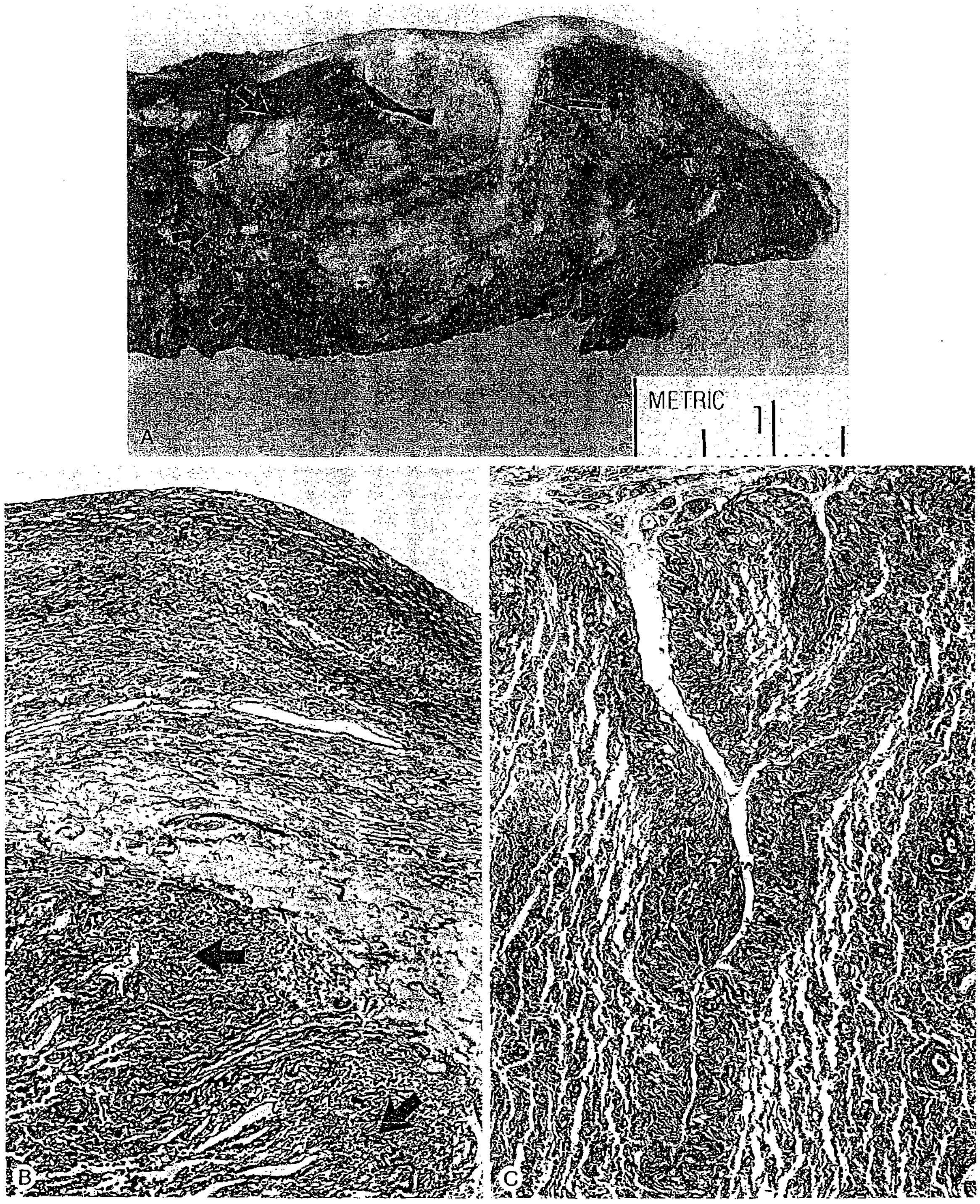

Figure 60–38. Round Atelectasis: Pathologic Characteristics. A slice of an uninflated lower lobe *(A)* shows a poorly defined, somewhat rounded focus of atelectasis *(short arrows)* that blends almost imperceptibly with normal lung. The overlying visceral pleura is fibrotic and focally invaginates into the underlying parenchyma *(long arrow)*. A histologic section *(B)* shows pleural fibrosis and wrinkling of the pleural elastic lamina *(arrows)*. A section through one of the deep pleural invaginations *(C)* reveals more extensive wrinkling. The adjacent lung is atelectatic and shows mild fibrosis. (*B*, ×60; *C*, ×40; both Verhoeff–van Gieson.) (From Menzies R, Fraser R: Round atelectasis. Am J Surg Pathol 11:674, 1987.)

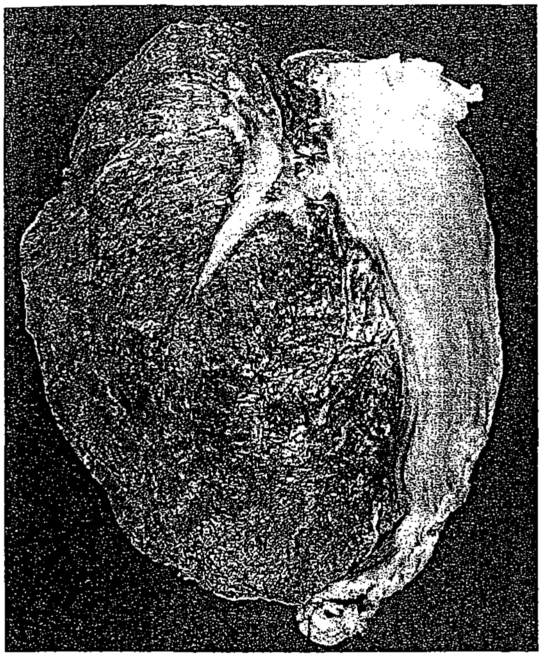

Figure 60–39. Round Atelectasis: Gross Appearance. A resected segment of lower lobe shows marked pleural fibrosis that is continuous with a somewhat triangular invagination that extends approximately 2 cm into the adjacent lung. The latter appears dense in the region of the invagination, reflecting the presence of atelectasis.

ribs.[449, 624, 633–635] The earliest manifestation is a thin line of unit density visible under a rib in the axillary region. Although usually multiple, occasionally only a single plaque is visible.

Because they frequently occur along the posterolateral and anterolateral portion of the thorax, plaques may be difficult to identify on posteroanterior and lateral radiographs, particularly when viewed *en face*. Sometimes, they are more readily detected on a tangential 45-degree oblique view.[624, 636, 637] Plaques may be bilateral and symmetric, bilateral and asymmetric or, less commonly, unilateral.[503, 638–640] For unexplained reasons, unilateral plaques are identified more commonly on the left (Fig. 60–41).[641] For example, in one review of radiographs of 105,064 civilian and military employees of the U.S. Navy, 1,914 were considered to have plaques, bilateral in 81% and unilateral in 19%;[639] in workers who had unilateral plaques, the left-to-right ratio was 3.5:1. In patients who have bilateral disease, the width and extent of plaques as well as the extent of calcification, are also frequently greater on the left than on the right, at least on radiographs.[640] In one study of CT scans from 40 patients who had asbestos-related plaques, there was no significant predominance in either hemithorax.[641a]

Although plaques usually involve the parietal pleura, they may also be seen in the visceral pleura, including the interlobar fissures (Fig. 60–42).[642] Thickening of fissures not related to plaques is also common. In a radiographic study of an asbestos-exposed population and a control group, thickening of the interlobar fissures was seen in 54% of asbestos workers compared with 16% in the unexposed control group.[642] Fissural thickening was present in 85% of workers who had parietal pleural plaques and in 36% of those without plaques; it was particularly common in patients who had pulmonary fibrosis (affecting 85%) but was also identified in 45% of those who did not have evidence of asbestosis.

Although the detection of plaques radiographically is highly specific for a history of asbestos exposure, the sensitivity is relatively poor. Depending on the criteria for diagnosis, the frequency with which plaques are recognized on the chest radiograph ranges from only 8% to 40% of cases in

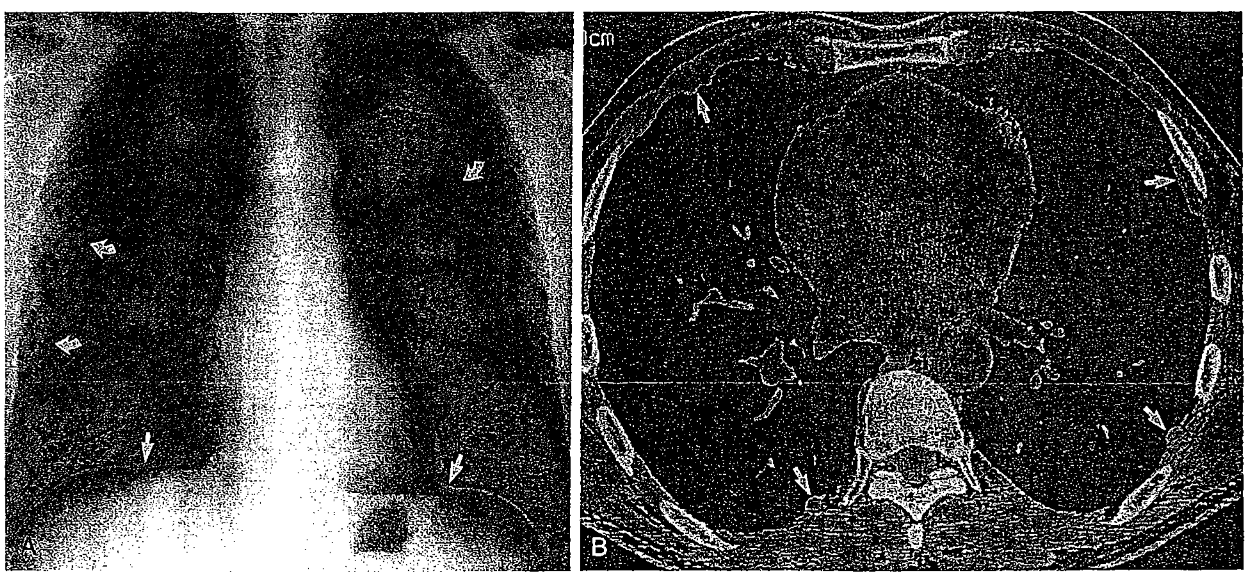

Figure 60–40. Pleural Plaques. A posteroanterior chest radiograph *(A)* demonstrates multiple pleural-based opacities along the chest wall and diaphragm. Several are viewed tangentially *(straight arrows)*, whereas others are ill-defined because they are viewed *en face (curved arrows)*, indicating their origin from the posterolateral or anterolateral chest wall. HRCT *(B)* confirms the presence of bilateral plaques *(arrows)*. The patient was a 51-year-old shipyard worker.

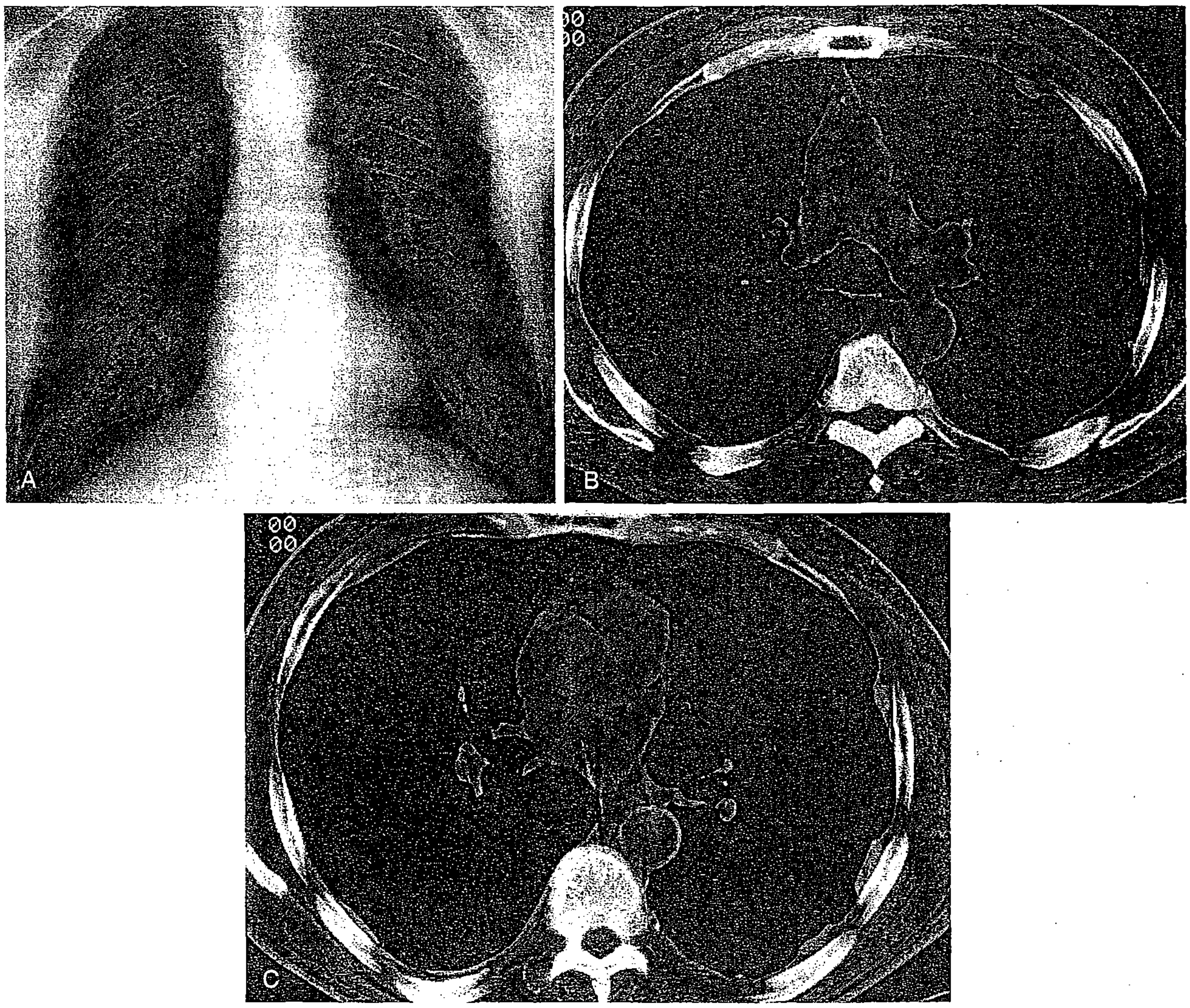

Figure 60–41. Markedly Asymmetric Pleural Plaques. A posteroanterior chest radiograph *(A)* in a 74-year-old shipyard worker shows evidence of pleural plaques only on the left side. HRCT at the level of the tracheal carina *(B)* also demonstrates only plaques on the left side. HRCT through the lower lung zones demonstrates prominent plaques on the left and thin plaques on the right.

which they are demonstrable at autopsy.[541] In one study, the combination of bilateral posterolateral plaques at least 5 mm thick or bilateral calcified diaphragmatic plaques was shown to have a 100% positive predictive value for the diagnosis of autopsy-proven asbestos-related pleural disease;[643] however, these criteria allowed detection of only 12% of plaques. Use of less strict criteria resulted in a considerable number of false-positive diagnoses.

The greatest problem in the radiographic diagnosis of pleural plaques (as well as diffuse pleural thickening) lies in distinguishing them from normal companion shadows of the chest wall—not those that are associated with the first three ribs (because this area is rarely involved in asbestos-related pleural disease), but those muscle and fat shadows that can be identified in as many as 75% of normal posteroanterior radiographs along the inferior convexity of the thorax. In fact, it is sometimes impossible to differentiate pleural plaques from companion shadows on the radiograph.

HRCT has a greater sensitivity than either conventional CT or chest radiography in the detection of these abnormalities.[627, 628, 644] With this technique, plaques can be identified as circumscribed areas of pleural thickening separated from the underlying rib and extrapleural soft tissues by a thin layer of fat (*see* Figs. 60–40 and 60–41). Normally, a 1- to 2-mm-thick stripe of soft tissue attenuation is visible on HRCT scans in the intercostal spaces at the point of contact between the lung and chest wall.[645] This stripe, called the *intercostal stripe*, consists of visceral and parietal pleura, endothoracic fascia, and the innermost portion of intercostal muscle. Most of the thickness of the stripe is related to the intercostal muscle because the endothoracic fascia is thin and the combined thickness of visceral and parietal pleura and normal fluid is only 0.2 to 0.4 mm.[645] The stripe can be seen because a layer of intercostal fat separates the innermost intercostal muscle from the internal intercostal muscles. Normally, no soft tissue attenuation is seen adjacent to a rib or